Docket No.: 231034US0

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF:	:	
Christophe BOULLE, et al.	:	EXAMINER: COTTON, ABIGAIL
SERIAL NO.: 10/670,327	:	
FILED: SEPTEMBER 26, 2003	:	GROUP ART UNIT: 1617

FOR: COMPOSITION CONTAINING A SECONDARY OR TERTIARY CARBONYL AMINE, METHOD OF USE THEREOF, COMPOUNDS

DECLARATION UNDER 37 C.F.R. 1.131

COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313

SIR:

I, Christophe KROMER, hereby declare:

1. I am a patent engineer employed by the assignee of the above-referenced patent application, L'Oréal.

2. Prior to October 1, 2002, a draft of the above-referenced patent application had been completed and had been forwarded to the inventors for review in France, a WTO member country. A copy of this draft application is attached at Tab A. An English translation of the draft application is attached at Tab B.

3. The draft application discloses using compounds falling within formula (I) of the above-identified application for anti-aging and anti-wrinkle purposes. (See, for example, Tab B at abstract and at page 2, last paragraph through page 6, first paragraph).

4. The undersigned petitioner declares further that all statements made herein of her own knowledge are true and that all statements made on information and belief are believe to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

5. Further deponent sayeth not.

KROMER Christophe
Name

Christophe KROMER.
Signature

July 26, 2006.
Date

ABREGE DESCRIPTIF

Composition, notamment cosmétique, comprenant une amine secondaire ou tertiaire carbonylée

La présente invention concerne une composition, adaptée à une application topique sur la peau, comprenant, dans un milieu physiologiquement acceptable, au moins une amine secondaire ou tertiaire carbonylée de formule donnée.

Elle concerne également l'utilisation d'une telle amine dans une composition adaptée à une application topique sur la peau, comme agent destiné à lisser les rides et ridules, en particulier les rides et ridules d'expression.

La présente invention concerne une composition, adaptée à une application topique sur la peau, comprenant, dans un milieu physiologiquement acceptable, au moins une amine secondaire ou tertiaire carbonylée de formule donnée. Elle concerne également l'utilisation d'une telle amine dans une composition adaptée à une application topique sur la peau, comme agent destiné à lisser les rides et ridules, en particulier les rides et ridules d'expression.

Les femmes, voire même les hommes, ont tendance actuellement à vouloir paraître jeunes le plus longtemps possible et cherchent par conséquent à estomper les marques du vieillissement de la peau, qui se traduisent notamment par des rides et des ridules. A ce sujet, la publicité et la mode font état de produits destinés à garder le plus longtemps possible une peau éclatante et sans ride, marques d'une peau jeune, d'autant plus que l'aspect physique agit sur le psychisme et/ou sur le moral.

Jusqu'à présent, on traitait les rides et les ridules à l'aide de produits cosmétiques contenant des actifs agissant sur la peau, par exemple en l'hydratant ou en améliorant son renouvellement cellulaire ou encore en favorisant la synthèse, ou en prévenant la dégradation, des fibres élastiques qui composent le tissu cutané.

Bien que ces traitements permettent d'agir sur les rides et ridules dues au vieillissement chronologique ou intrinsèque, ainsi que sur celles dues au photo-vieillissement, ils n'ont pas d'effet sur les rides et ridules d'expression, lesquelles nécessitent une intervention sur la composante contractile musculaire des rides présente dans la peau.

Jusqu'à présent, le seul moyen couramment utilisé pour agir sur les rides d'expression est la toxine botulique qui est notamment injectée dans les rides de la glabelle qui sont les rides inter-sourcillières (voir J.D. Carruters et al., J. Dermatol. Surg. Oncol., 1992, 18, pp. 17-21).

La Demanderesse a en outre proposé divers composés susceptibles d'offrir un effet myorelaxant lorsqu'ils sont appliqués topiquement sur la peau, permettant ainsi d'agir par une autre voie sur les rides d'expression. Parmi ces composés, on peut notamment citer les antagonistes des récepteurs associés aux canaux calciques (FR-2 793 681), et en particulier le manganèse et ses sels (FR-2 809 005) et l'alvérine (FR-2

798 590) ; et les agonistes des récepteurs associés aux canaux chlore, dont la glycine (EP-0 704 210) et certains extraits d'Iris pallida (FR-2 746 641).

Il reste toutefois le besoin de disposer de composés efficaces pour lisser ou estomper les rides et ridules d'expression.

Or, la Demanderesse a découvert avec étonnement que certaines amines secondaires et tertiaires permettaient de satisfaire ce besoin.

On connaît, certes, du document EP-1 090 630 certaines amines secondaires et tertiaires ayant la propriété d'augmenter la synthèse de collagène par les fibroblastes et d'hydrater la peau, utiles contre la peau sèche et la dermatite atopique, et qui ont également une efficacité sur les rides. Toutefois, les amines carbonylées citées dans ce document ne comportent pas de groupe phényle et sont telles que le groupe carbonyle est directement adjacent à l'atome d'azote. En outre, elles n'ont pas d'effet sur les rides et ridules d'expression.

On connaît par ailleurs du document WO 93/05763 certaines amines di- et tri-substituées par au moins deux chaînes portant chacune au moins un groupe hydroxy. Ces amines augmentent la différenciation des kératinocytes, limitent l'épaississement UV-induit de l'épiderme et sont utiles pour prévenir et traiter les rides induites par le rayonnement UVB. Il n'est pas suggéré que ces amines, différentes de celles objet de la présente invention en ce sens qu'elles ne comprennent pas de groupement carbonyle, aient un quelconque effet sur les rides et ridules d'expression.

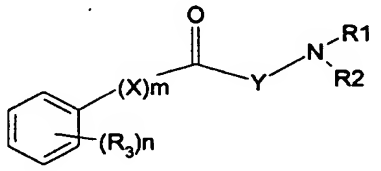
De manière analogue, le document EP-0 691 327 divulgue une famille très vaste d'amines mono-, di- ou trisubstituées décrites comme efficaces pour lisser les rides. Les amines exemplifiées dans cette demande de brevet ne sont pas substituées par des chaînes susceptibles de comprendre un groupement carbonyle, contrairement aux amines objet de la présente invention. En outre, il n'est pas suggéré qu'elles aient un quelconque effet sur les rides et ridules d'expression.

La Demanderesse a maintenant découvert qu'en sélectionnant certaines amines secondaires et tertiaires carbonylées de structure simple, il était possible d'obtenir des compositions cosmétiques efficaces pour lisser les rides et ridules d'expression.

Il a, certes, été décrit précédemment par la Demanderesse l'utilisation de l'alvérine, qui est une amine trisubstituée, comme agent myorelaxant destiné à lisser les rides d'expression. Toutefois, à la différence des composés objet de la présente invention, l'alvérine ne renferme pas de groupement carbonyle. Or, il n'était pas évident que l'activité myorelaxante de l'alvérine soit conservée par introduction de groupements carbonyle dans sa molécule.

[cet argument mériterait d'être développé...]

La présente invention a donc pour objet une composition, adaptée à une application topique sur la peau, comprenant, dans un milieu physiologiquement acceptable, au moins un composé de formule (I) :



(I)

dans laquelle :

R_1 désigne un atome d'hydrogène ou un groupe alkyle linéaire ou ramifié, saturé ou insaturé, en C_1-C_8, ***(éventuellement substitué ?)***

R_2 désigne un groupe alkyle linéaire ou ramifié, saturé ou insaturé, en C_1-C_{20}, éventuellement substitué,

R_3 désigne un groupe alkyle linéaire ou ramifié, saturé ou insaturé, ***(de quelle longueur ?)***, un groupe –OR, -SR, -NRR', -COOR ou $-CF_3$ ou un atome d'halogène, où R et R' désignent indépendamment un atome d'hydrogène ou un groupe alkyle en C_1-C_4, linéaire ou ramifié, ou un groupe aryle,

X est un groupe alkyle en C_1-C_9, saturé ou insaturé, éventuellement substitué,

Y est un groupe alkyle en C_1-C_{10}, saturé ou insaturé, éventuellement substitué,

les substituants de R_2, X et Y étant indépendamment choisis parmi : par un groupe alkyle, -OR, -SR, -NRR', -COOR, =O, aryle, arylcarbonyle, alkylcarbonyle, où R et R' ont la signification donnée ci-dessus,

m est 0 ou 1,

n est compris entre 0 et 3,

ou son sel d'addition avec un acide.

Dans la formule (I), les groupes alkyle peuvent être choisis, selon le cas, parmi les groupes : méthyle, éthyle, n-propyle, isopropyle, n-butyle, isobutyle, tert-butyle, pentyle, hexyle, heptyle, octyle, nonyle, décyle, undécyle, dodécyle, myristyle, palmityle, stéaryle et arachidyle.

De son côté, le groupe aryle peut être choisi parmi un groupe benzyle et un groupe phényle.

L'atome d'halogène peut être un atome de fluor, de chlore, de brome ou d'iode.

Comme sels du composé de formule (I), on peut citer les sels obtenus par addition du composé de formule (I) avec un acide inorganique, choisi notamment parmi les acides chlorhydrique, sulfurique, nitrique et phosphorique, ou avec un acide organique, choisi en particulier parmi les acides succinique, fumarique, lactique, glycolique, citrique et tartrique.

Les composés de formule (I) peuvent notamment être préparés comme décrit dans BADOSOV. E. P. et al, Chemistry of β-Amino Ketones, VII. Synthesis of Substituted Methyl and Phenyl β-[N-methyl-N(β-acetylethyl)]aminoethyl ketones by aminomethylation of ketones with formaldehyde and the salts of methyl and phenyl β-methylaminoalkyl ketones, ***(à compléter)***, également publié dans Zhurnal Organicheskoi Khimii, Vol. 11, No. 5, pp. 972-977, Mai 1975. La synthèse de ces composés a par ailleurs été décrite dans VON K. THIELE et al., Neue Piperidinderivative aus herzwirksamen –Aminoketonen, ***(à compléter)***.
[je ne vois pas de quels ouvrages les deux publications que vous m'avez envoyées le 19 septembre par fax sont extraites]

Selon une forme d'exécution préférée de l'invention, le composé de formule (I) est tel que l'une au moins des conditions suivantes, et de préférence toutes ces conditions, sont satisfaites :

- m = 0
- n = 0

- Y est un groupe alkyle en C_1-C_3,
- R_1 est un groupe alkyle en C_1-C_3,
- R_2 est un groupe alkyle en C_1-C_3 substitué par un groupe arylcarbonyle

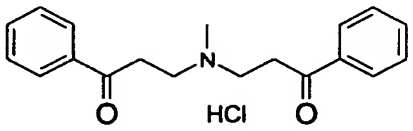
dans la formule (I), ou son sel avec un acide inorganique.

De façon plus préférentielle encore, le composé de formule (I) est tel que :

- m = 0
- n = 0
- Y est un groupe éthyle,
- R_1 est un groupe méthyle, et
- R_2 est un groupe éthyle substitué par un groupe benzoyle

dans la formule (I), ou son sel avec l'acide chlorhydrique.

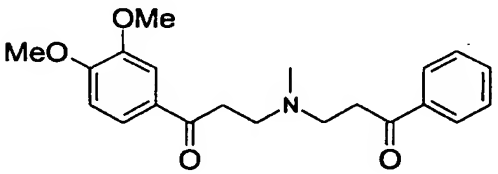
Un tel composé, qui répond à la formule (Ia) ci-dessous :



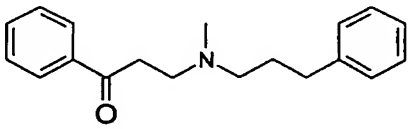
(Ia)

est notamment disponible auprès de la société SALOR sous la référence commerciale S35,861-4. Il peut en variante être préparé par aminométhylation d'acétophénone à l'aide du chlorhydrate de 3-méthylamino-1-phenyl-1-propanone (obtenu lui-même par réaction de la méthylamine sur la phenyl isopropényl cétone) et de formaldéhyde, comme décrit dans la première publication indiquée plus haut.

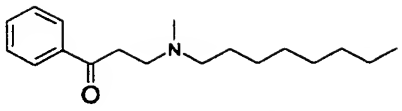
D'autres exemples de composés de formule (I) utiles dans la présente invention comprennent les composés (Ib) à (Ij) suivants :



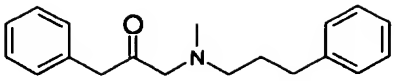
(Ib)



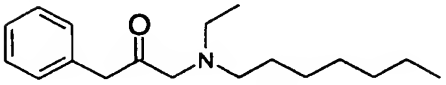
(Ic)



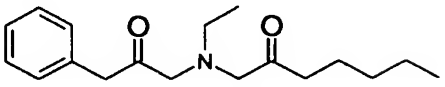
(Id)



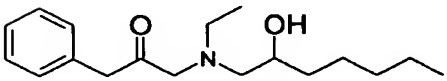
(Ie)



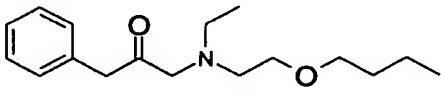
(If)



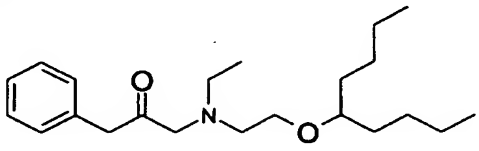
(Ig)



(Ih)



(Ii)



(Ij)

Comme cela sera démontré dans les Exemples ci-après, la Demanderesse a mis en évidence un effet myorelaxant des composés de formule (I) selon l'invention, qui permet d'envisager leur utilisation, plus particulièrement dans le lissage des rides et ridules d'expression.

La quantité de composé(s) de formule (I) utilisable selon l'invention est bien entendu fonction de l'effet recherché et peut donc varier dans une large mesure.

Pour donner un ordre de grandeur, on peut utiliser ce composé en une quantité représentant de 0,01% à 10% du poids total de la composition, préférentiellement en une quantité représentant de 0,05% à 5% du poids total de la composition, plus préférentiellement en une quantité représentant de 0,1% à 2% du poids total de la composition.

La composition selon l'invention est adaptée à une application topique sur la peau et elle contient donc un milieu physiologiquement acceptable, c'est-à-dire compatible

avec la peau et éventuellement avec ses phanères (cils, ongles, cheveux) et/ou les muqueuses.

Cette composition peut se présenter sous toutes les formes galéniques normalement utilisées dans le domaine cosmétique , et elle peut être notamment sous forme d'une solution aqueuse éventuellement gélifiée, d'une dispersion du type lotion éventuellement biphasée, d'une émulsion obtenue par dispersion d'une phase grasse dans une phase aqueuse (H/E) ou inversement (E/H), ou d'une émulsion triple (E/H/E ou H/E/H) ou d'une dispersion vésiculaire de type ionique et/ou non ionique. Ces compositions sont préparées selon les méthodes usuelles. On préfère utiliser selon cette invention une composition sous la forme d'une émulsion huile-dans-eau.

Cette composition peut être plus ou moins fluide et avoir l'aspect d'une crème blanche ou colorée, d'une pommade, d'un lait, d'une lotion, d'un sérum, d'une pâte, d'une mousse. Elle peut éventuellement être appliquée sous forme d'aérosol. Elle peut également se présenter sous forme solide, en particulier sous forme de stick. Elle peut être utilisée comme produit de soin et/ou comme produit de maquillage pour la peau.

De façon connue, la composition utilisée selon l'invention peut contenir également les adjuvants habituels dans le domaine cosmétique, tels que les gélifiants hydrophiles ou lipophiles, les actifs hydrophiles ou lipophiles, les conservateurs, les antioxydants, les solvants, les parfums, les charges, les filtres, les pigments, les absorbeurs d'odeur et les matières colorantes. Les quantités de ces différents adjuvants sont celles classiquement utilisées dans le domaine considéré, et par exemple de 0,01 à 20% du poids total de la composition. Ces adjuvants, selon leur nature, peuvent être introduits dans la phase grasse, dans la phase aqueuse ou dans les vésicules lipidiques. En tout état de cause, ces adjuvants, ainsi que leurs proportions, seront choisis de manière à ne pas nuire aux propriétés recherchées des composés de formule (I) selon l'invention.

Lorsque la composition utilisée selon l'invention est une émulsion, la proportion de la phase grasse peut aller de 5 à 80 % en poids, et de préférence de 5 à 50 % en poids par rapport au poids total de la composition. Les huiles, les émulsionnants et les coémulsionnants utilisés dans la composition sous forme d'émulsion sont choisis parmi ceux classiquement utilisés dans le domaine considéré. L'émulsionnant et le coémulsionnant sont présents, dans la composition, en une proportion allant de 0,3 à

30 % en poids, et de préférence de 0,5 à 20 % en poids par rapport au poids total de la composition.

Comme huiles utilisables dans l'invention, on peut citer les huiles minérales (huile de vaseline), les huiles d'origine végétale (huile d'avocat, huile de soja), les huiles d'origine animale (lanoline), les huiles de synthèse (perhydrosqualène), les huiles siliconées (cyclométhicone) et les huiles fluorées (perfluoropolyéthers). On peut aussi utiliser comme matières grasses des alcools gras (alcool cétylique), des acides gras, des cires (cire de carnauba, ozokérite).

Comme émulsionnants et coémulsionnants utilisables dans l'invention, on peut citer par exemple les esters d'acide gras et de polyéthylène glycol tels que le stéarate de PEG-100, et les esters d'acide gras et de glycérine tels que le stéarate de glycéryle.

Comme gélifiants hydrophiles, on peut citer en particulier les polymères carboxyvinyliques (carbomer), les copolymères acryliques tels que les copolymères d'acrylates/alkylacrylates, les polyacrylamides, les polysaccharides, les gommes naturelles et les argiles, et, comme gélifiants lipophiles, on peut citer les argiles modifiées comme les bentones, les sels métalliques d'acides gras, la silice hydrophobe et les polyéthylènes.

Comme actifs, il sera avantageux d'introduire dans la composition utilisée selon l'invention au moins un composé choisi parmi : les agents desquamants ; les agents hydratants ; les agents dépigmentants ou propigmentants ; les agents anti-glycation ; les inhibiteurs de NO-synthase ; les agents stimulant la synthèse de macromolécules dermiques ou épidermiques et/ou empêchant leur dégradation ; les agents stimulant la prolifération des fibroblastes et/ou des kératinocytes ou stimulant la différenciation des kératinocytes ; les agents myorelaxants ; les agents tenseurs ; les agents anti-pollution et/ou anti-radicalaire ; les agents agissant sur la microcirculation ; les agents agissant sur le métabolisme énergétique des cellules ; et leurs mélanges.

Des exemples de tels composés additionnels sont donnés ci-dessous.

1. Agents desquamants

Par "agent desquamant", on entend tout composé capable d'agir :

- soit directement sur la desquamation en favorisant l'exfoliation, tel que les β-hydroxyacides, en particulier l'acide salicylique et ses dérivés (dont l'acide n-octanoyl 5-salicylique) ; les α-hydroxyacides, tels que les acides glycolique, citrique, lactique, tartrique, malique ou mandélique ; l'urée ; l'acide gentisique ; les oligofucoses ; l'acide cinnamique ; l'extrait de Saphora japonica ; le resvératrol ;

- soit sur les enzymes impliquées dans la desquamation ou la dégradation des cornéodesmosomes, les glycosidases, la stratum corneum chymotryptic enzym (SCCE) voire d'autres protéases (trypsine, chymotrypsine-like). On peut citer les agents chélatant des sels minéraux: l'EDTA ; l'acide N-acyl-N,N',N' éthylène diaminetriacétique ; les composés aminosulfoniques et en particulier l'acide (N-2 hydroxyéthylpiperazine-N-2-éthane) sulfonique (HEPES) ; les dérivés de l'acide 2-oxothiazolidine-4-carboxylique (procystéine) ; les dérivés d'acides alpha aminés de type glycine (tels que décrits dans EP-0 852 949, ainsi que le méthyl glycine diacétate de sodium commercialisé par BASF sous la dénomination commerciale TRILON M) ; le miel ; les dérivés de sucre tels que l'O-octanoyl-6-D-maltose et la N-acétyl glucosamine.

2. Agent hydratant

Par "agent hydratant", on entend :

- soit un composé agissant sur la fonction barrière, en vue de maintenir l'hydratation du stratum corneum, ou un composé occlusif. On peut citer les céramides, les composés à base sphingoïde, les lécithines, les glycosphingolipides, les phospholipides, le cholestérol et ses dérivés, les phytostérols (stigmastérol, β-sitostérol, campestérol), les acides gras essentiels, le 1-2 diacylglycérol, la 4-chromanone, les triterpènes pentacycliques tels que l'acide ursolique, la vaseline et la lanoline ;

- soit un composé augmentant directement la teneur en eau du stratum corneum, tel que le thréalose et ses dérivés, l'acide hyaluronique et ses dérivés, le glycérol, le pentanediol, le pidolate de sodium, la sérine, le xylitol, le lactate de sodium, le

polyacrylate de glycérol, l'ectoïne et ses dérivés, le chitosane, les oligo- et polysaccharides, les carbonates cycliques, l'acide N-lauroyl pyrrolidone carboxylique, et la N-α-benzoyl-L-arginine ;

- soit un composé activant les glandes sébacées tel que la DHEA et ses dérivés, et la vitamine D et ses dérivés.

3. Agent dépigmentant ou pro-pigmentant

Les agents dépigmentants susceptibles d'être incorporés dans la composition selon la présente invention comprennent par exemple les composés suivants : l'acide kojique ; l'acide ellagique ; l'arbutine et ses dérivés tels que ceux décrits dans les demandes EP-895 779 et EP-524 109 ; l'hydroquinone ; les dérivés d'aminophénol tels que ceux décrits dans les demandes WO 99/10318 et WO 99/32077, et en particulier le N-cholestéryloxycarbonyl-para-aminophénol et le N-éthyloxycarbonyl-para-aminophénol ; les dérivés d'iminophénol, en particulier ceux décrits dans la demande WO 99/22707 ; l'acide L-2-oxothiazolidine-4-carboxylique ou procystéine, ainsi que ses sels et esters ; l'acide ascorbique et ses dérivés, notamment le glucoside d'ascorbyle ; et les extraits de plantes, en particulier de réglisse, de mûrier et de scutellaire, sans que cette liste soit limitative.

Comme agent pro-pigmentant, on peut citer l'extrait de pimprenelle (Sanguisorba officinalis) commercialisé par la société MARUZEN et les extraits de chrysanthème (Chrysanthemum morifolium).

4. Agent anti-glycation

Par "agent anti-glycation", on entend un composé prévenant et/ou diminuant la glycation des protéines de la peau, en particulier des protéines du derme telles que le collagène.

Des exemples d'agents anti-glycation sont les extraits végétaux de la famille des Ericaceae, tels qu'un extrait de myrtille (*Vaccinium angustifolium*) ; l'ergothionéine et ses dérivés ; et les hydroxystilbènes et leurs dérivés, tels que le resvératrol et le 3,3', 5,5'-tétrahydroxystilbène.

5. Inhibiteur de NO-synthase

Des exemples d'inhibiteurs de NO-synthase convenant à une utilisation dans la présente invention comprennent notamment un extrait de végétal de l'espèce *Vitis vinifera* qui est notamment commercialisé par la société Euromed sous la dénomination Leucocyanidines de raisins extra, ou encore par la société Indena sous la dénomination Leucoselect®, ou enfin par la société Hansen sous la dénomination Extrait de marc de raisin ; un extrait de végétal de l'espèce *Olea europaea* qui est de préférence obtenu à partir de feuilles d'olivier et est notamment commercialisé par la société VINYALS sous forme d'extrait sec, ou par la société Biologia & Technologia sous la dénomination commerciale Eurol BT ; et un extrait d'un végétal de l'espèce *Gingko biloba* qui est de préférence un extrait aqueux sec de ce végétal vendu par la société Beaufour sous le nom commercial Ginkgo biloba extrait standard.

6. Agent stimulant la synthèse de macromolécules dermiques ou épidermiques et/ou empêchant leur dégradation

Parmi les actifs stimulant les macromolécules du derme ou empêchant leur dégradation, on peut citer ceux qui agissent :

- soit sur la synthèse du collagène, tels que les extraits de Centella asiatica ; les asiaticosides et dérivés ; l'acide ascorbique ou vitamine C et ses dérivés ; les peptides de synthèse tels que la lamin, le biopeptide CL ou palmitoyloligopeptide commercialisé par la société SEDERMA ; les peptides extraits de végétaux, tels que l'hydrolysat de soja commercialisé par la société COLETICA sous la dénomination commerciale Phytokine® ; et les hormones végétales telles que les auxines.

- soit sur la synthèse d'élastine, tels que l'extrait de Saccharomyces Cerivisiae commercialisé par la société LSN sous la dénomination commerciale Cytovitin® ; et l'extrait d'algue Macrocystis pyrifera commercialisé par la société SECMA sous la dénomination commerciale Kelpadelie® ;

- soit sur la synthèse des glycosaminoglycanes, tels que le produit de fermentation du lait par lactobacillus vulgaris, commercialisé par la société BROOKS sous la

dénomination commerciale Biomin yogourth® ; l'extrait d'algue brune Padina pavonica commercialisé par la société ALBAN MÜLLER sous la dénomination commerciale HSP3® ; et l'extrait de Saccharomyces cerevisiae disponible notamment auprès de la société SILAB sous la dénomination commerciale Firmalift® ou auprès de la société LSN sous la dénomination commerciale Cytovitin® ;

- soit sur la synthèse de la fibronectine, tels que l'extrait de zooplancton Salina commercialisé par la société SEPORGA sous la dénomination commerciale GP4G® ; l'extrait de levure disponible notamment auprès de la société ALBAN MÜLLER sous la dénomination commerciale Drieline® ; et le palmitoyl pentapeptide commercialisé par la société SEDERMA sous la dénomination commerciale Matrixil® ;

- soit sur l'inhibition des métalloprotéinases (MMP) telles que plus particulièrement les MMP 1, 2, 3, 9 . On peut citer : les rétinoïdes et dérivés, les oligopeptides et les lipopeptides, les lipoaminoacides, l'extrait de malt commercialisé par la société COLETICA sous la dénomination commerciale Collalift® ; les extraits de myrtille ou de romarin ; le lycopène ; les isoflavones, leurs dérivés ou les extraits végétaux en contenant, en particulier les extraits de soja (commercialisé par exemple par la société ICHIMARU PHARCOS sous la dénomination commerciale Flavostérone SB®), de trèfle rouge, de lin, de kakkon ou de sauge ;

- soit sur l'inhibition des sérine protéases telles que l'élastase leucocytaire ou la cathepsine G. On peut citer : l'extrait peptidique de graines de légumineuse (Pisum sativum) commercialisé par la société LSN sous la dénomination commerciale Parelastyl® ; les héparinoïdes ; et les pseudodipeptides.

Parmi les actifs stimulant les macromolécules épidermiques, telles que la fillagrine et les kératines, on peut citer notamment l'extrait de lupin commercialisé par la société SILAB sous la dénomination commerciale Structurine® ; l'extrait de bourgeons de hêtre Fagus sylvatica commercialisé par la société GATTEFOSSE sous la dénomination commerciale Gatuline® ; et l'extrait de zooplancton Salina commercialisé par la société SEPORGA sous la dénomination commerciale GP4G®.

7. Agent stimulant la prolifération des fibroblastes ou des kératinocytes et/ou la différenciation des kératinocytes

Les agents stimulant la prolifération des fibroblastes utilisables dans la composition selon l'invention peuvent par exemple être choisis parmi les protéines ou polypeptides végétaux, extraits notamment du soja (par exemple un extrait de soja commercialisé par la société LSN sous la dénomination Eleseryl SH-VEG 8® ou commercialisé par la société SILAB sous la dénomination commerciale Raffermine®) ; et les hormones végétales telles que les giberrellines et les cytokinines.

Les agents stimulant la prolifération des kératinocytes, utilisables dans la composition selon l'invention, comprennent notamment les rétinoïdes tels que le rétinol et ses esters, dont le palmitate de rétinyle ; le phloroglucinol ; les extraits de tourteaux de noix commercialisés par la société GATTEFOSSE ; et les extraits de Solanum tuberosum commercialisés par la société SEDERMA.

Les agents stimulant la différenciation des kératinocytes comprennent par exemple les minéraux tels que le calcium ; l'extrait de lupin commercialisé par la société SILAB sous la dénomination commerciale Photopréventine®; le beta-sitosteryl sulfate de sodium commercialisé par la société SEPORGA sous la dénomination commerciale Phytocohésine® ; et l'extrait de maïs commercialisé par la société SOLABIA sous la dénomination commerciale Phytovityl®.

8. Agent myorelaxant

Outre le composé de formule (I) décrit précédemment, la composition selon l'invention peut comprendre d'autres agents myorelaxants, parmi lesquels on peut citer en particulier l'alvérine et ses sels, notamment le citrate d'alvérine, le gluconate de manganèse, les sapogénines telles que la diosgénine et les extraits naturels en contenant (tels que les extraits de Wild Yam), ainsi que l'hexapeptide argireline R commercialisé par la société LIPOTEC.

9. Agent tenseur

Par "agent tenseur", on entend un composé capable d'exercer une traction sur la peau, qui a pour effet d'estomper temporairement les irrégularités de la surface de la peau, telles que les rides et ridules.

Parmi les agents tenseurs utilisables dans la composition selon la présente invention, on peut citer notamment :

(1) les polymères synthétiques, tels que les latex de polyuréthanne ou les latex acrylique-silicone, en particulier ceux décrits dans la demande de brevet EP-1038519, tels qu'un polydiméthyl siloxane greffé propylthio(polyacrylate de méthyle), propylthio(polyméthacrylate de méthyle) et propylthio(polyacide méthacrylique), ou encore un polydiméthyl siloxane greffé propylthio(polyméthacrylate d'isobutyle) et propylthio(polyacide méthacrylique). De tels polymères siliconés greffés sont notamment vendus par la Société 3M sous les dénominations commerciales VS 80, VS 70 ou LO21,

(2) les polymères d'origine naturelle, notamment (a) les polyholosides, par exemple (i) sous forme d'amidon issu notamment de riz, de maïs, de pomme de terre, de manioc, de pois, de froment, d'avoine, etc... ou (ii) sous forme de carraghénanes, alginates, agars, gellanes, polymères cellulosiques et pectines, avantageusement en dispersion aqueuse de microparticules de gel, et (b) les latex constitués par la résine shellac, la gomme de sandaraque, les dammars, les élémis, les copals, les dérivés cellulosiques, et leurs mélanges,

(3) les protéines et hydrolysats de protéines végétales, en particulier de maïs, de seigle, de froment, de sarrasin, de sésame, d'épautre, de pois, de fève, de lentille, de soja et de lupin,

(3) les silicates mixtes, notamment les phyllosilicates et en particulier les Laponites,

(4) les microparticules de cire, choisies par exemple parmi les cires de Carnauba, de Candelila ou d'Alfa,

(5) les particules colloïdales de charge inorganique ayant un diamètre moyen en nombre compris entre 0,1 et 100 nm, de préférence entre 3 et 30 nm, et choisies par exemple parmi : la silice, l'oxyde de cérium, l'oxyde de zirconium, l'alumine, le carbonate de calcium, le sulfate de baryum, le sulfate de calcium, l'oxyde de zinc et le dioxyde de titane.

10. Agent anti-pollution ou anti-radicalaire

Par l'expression "agent anti-pollution", on entend tout composé capable de piéger l'ozone, les composés aromatiques mono- ou polycycliques tels que le benzopyrène et/ou les métaux lourds tels que le cobalt, le mercure, le cadmium et/ou le nickel. Par "agent anti-radicalaire", on entend tout composé capable de piéger les radicaux libres.

Comme agents piégeurs d'ozone utilisables dans la composition selon l'invention, on peut citer en particulier la vitamine C et ses dérivés dont le glucoside d'ascorbyle ; les phénols et polyphénols, en particulier les tannins, l'acide ellagique et l'acide tannique ; l'épigallocatéchine et les extraits naturels en contenant ; les extraits de feuille d'olivier ; les extraits de thé, en particulier de thé vert ; les anthocyanes ; les extraits de romarin ; les acides phénols, en particulier l'acide chorogénique ; les stilbènes, en particulier le resvératrol ; les dérivés d'acides aminés soufrés, en particulier la S-carboxyméthylcystéine ; l'ergothionéine ; la N-acétylcystéine ; des chélatants comme la N,N'-bis-(3,4,5-triméthoxybenzyl)éthylènediamine ou l'un de ses sels, complexes métalliques ou esters ; des caroténoïdes tels que la crocétine ; et des matières premières diverses comme le mélange d'arginine, ribonucléate d'histidine, mannitol, adénosinetriphosphate, pyridoxine, phénylalanine, tyrosine et ARN hydrolysé commercialisé par les Laboratoires Sérobiologiques sous la dénomination commerciale CPP LS 2633-12F®, la fraction hydrosoluble de maïs commercialisée par la société SOLABIA sous la dénomination commerciale Phytovityl®, le mélange d'extrait de fumeterre et d'extrait de citron commercialisé sous la dénomination Unicotrozon C-49® par la société Induchem, et le mélange d'extraits de ginseng, de pomme, de pêche, de blé et d'orge vendu par la société PROVITAL sous la dénomination commerciale Pronalen Bioprotect®.

Comme agents piégeurs de composés aromatiques mono- ou polycycliques utilisables dans la composition selon l'invention, on peut citer en particulier les tannins tels que l'acide ellagique ; les dérivés indoles, en particulier l'indol-3-carbinol ; les extraits de thé en particulier de thé vert, les extraits de Jacinthe d'eau ou eichornia crassipes ; et la fraction hydrosoluble de maïs commercialisée par la société SOLABIA sous la dénomination commerciale Phytovityl®.

Enfin, comme agents piégeurs de métaux lourds utilisables dans la composition selon l'invention, on peut citer en particulier les agents chélatants tels que l'EDTA, le sel

pentasodique d'éthylènediamine tétraméthylène phosphonique, et la N,N'-bis-(3,4,5-triméthoxybenzyl)éthylènediamine ou l'un de ses sels, complexes métalliques ou esters ; l'acide phytique ; les dérivés de chitosan ; les extraits de thé, en particulier de thé vert ; les tannins tels que l'acide ellagique ; les acides aminés soufrés tels que la cystéine ; les extraits de Jacinthe d'eau (Eichornia crassipes) ; et la fraction hydrosoluble de maïs commercialisée par la société SOLABIA sous la dénomination commerciale Phytovityl®.

Les agents anti-radicalaires utilisables dans la composition selon l'invention comprennent, outre certains agents anti-pollution mentionnés précédemment, la vitamine E et ses dérivés tels que l'acétate de tocophéryle ; les bioflavonoïdes ; le co-enzyme Q10 ou ubiquinone ; certaines enzymes comme la catalase, le superoxyde dismutase, la lactoperoxydase, le glutathion peroxydase et les quinones réductases ; le glutathion ; le benzylidène camphre ; les benzylcyclanones ; les naphtalénones substituées ; les pidolates ; le phytantriol ; le gamma-oryzanol ; les lignanes ; et la mélatonine.

11. Les agents agissant sur la microcirculation

Les actifs agissant sur la microcirculation (vasoprotecteurs ou vasodilatateurs), se trouvent notamment parmi les flavonoïdes, les ruscogénines, les esculosides, l'escine extraite du marron d'Inde, les nicotinates, l'héperidine méthyl chalcone, les huiles essentielles de lavande ou de romarin, les extraits de *Ammi Visnaga*.

12. Les agents agissant sur le métabolisme énergétique des cellules

Par cette expression, on entend les actifs agissant sur le métabolisme énergétique cutané tel que, par exemple, et de façon non limitative, la synthèse d'ATP, ainsi que ceux qui interviennent sur la chaîne respiratoire de la cellule ou sur les réserves énergétiques. On peut citer à ce titre le Coenzyme Q10 (ubiquinone), le cytochrome C, la créatine ou encore la phosphocréatine.

Comme indiqué précédemment, la composition selon l'invention peut également renfermer des filtres UVA et/ou UVB, sous forme de composés organiques ou

inorganiques, ces derniers étant éventuellement enrobés pour les rendre hydrophobes.

Les filtres organiques peuvent notamment être choisis parmi : les anthranilates, en particulier l'anthranilate de menthyle ; les benzophénones, en particulier la benzophénone-1, la benzophénone-3, la benzophénone-5, la benzophénone-6, la benzophénone-8, la benzophénone-9, la benzophénone-12, et préférentiellement la Benzophénone-3 (Oxybenzone), ou la Benzophénone-4 (Uvinul MS40 disponible chez B.A.S.F.) ; les benzylidènes-camphres, en particulier le 3-benzylidène-camphre, l'acide benzylidènecampho-sulfonique, le benzalkoniumméthosulfate de camphre, le polyacrylamidométhylbenzylidène camphre, l'acide téréphthalylidène di-camphre sulfonique, et préférentiellement le 4-méthylbenzylidène camphre (Eusolex 6300 disponible chez Merck) ; les benzimidazoles, en particulier le benzimidazilate (Neo Heliopan AP disponible chez Haarmann et Reimer), ou l'acide phénylbenzimidazole sulfonique (Eusolex 232 disponible chez Merck) ; les benzotriazoles, en particulier le drométrizole trisiloxane, ou le méthylène bis-benzotriazolyltétraméthylbutylphénol (Tinosorb M disponible chez Ciba) ; les cinnamates, en particulier le cinoxate, le DEA méthoxycinnamate, le méthylcinnamate de diisopropyle, le glycéryl éthylhexanoate de diméthoxycinnamate, le méthoxycinnamate d'isopropyle, le cinnamate d'isoamyle, et préférentiellement l'éthocrylène (Uvinul N35 disponible chez B.A.S.F.), l'octylméthoxycinnamate (Parsol MCX disponible chez Hoffmann La Roche), ou l'octocrylène (Uvinul 539 disponible chez B.A.S.F.) ; les dibenzoylméthanes, en particulier le butyl méthoxydibenzoylméthane (Parsol 1789) ; les imidazolines, en particulier l'éthylhexyl diméthoxybenzylidène dioxoimidazoline ; les PABA, en particulier l'éthyl Dihydroxypropyl PABA, l'éthylhexyldiméthyl PABA, le glycéryl PABA, le PABA, le PEG-25 PABA, et préférentiellement la diéthylhexylbutamido-triazone (Uvasorb HEB disponible chez 3V Sigma), l'éthylhexyltriazone (Uvinul T150 disponible chez B.A.S.F.), ou l'éthyl PABA (benzocaïne) ; les salicylates, en particulier le salicyclate de dipropylèneglycol, le salicylate d'éthylhexyle, l'homosalate, ou le TEA salicylate ; les triazines, en particulier l'anisotriazine (Tinosorb S disponible chez Ciba) ; le drometrizole trisiloxane.

Les filtres inorganiques sont de préférence constitués d'oxyde de zinc et/ou de dioxyde de titane, de préférence de taille nanométrique, éventuellement enrobés d'alumine et/ou d'acide stéarique.

L'invention a donc aussi pour objet l'utilisation cosmétique d'au moins un composé de formule (I) tel que défini ci-dessus, dans une composition adaptée à une application topique sur la peau, comme agent destiné à lisser les rides et ridules, en particulier d'expression.

Elle a encore pour objet un procédé de traitement cosmétique d'une peau ridée, comprenant l'application topique sur ladite peau d'une composition telle que définie précédemment.

La composition selon l'invention est donc avantageusement destinée à être appliquée sur les zones du visage ou du front marquées par des rides et ridules d'expression, et/ou sur les personnes présentant des rides et ridules d'expression.

Les rides et ridules concernées sont de préférence celles disposées radialement autour de la bouche et/ou des yeux, en particulier les rides de la patte d'oie, et/ou situées au niveau du front, en particulier la ride dite du lion, située au niveau de la glabelle, dans l'espace inter-sourcillier, et/ou disposées horizontalement sur le front.

L'invention sera maintenant illustrée par les exemples non limitatifs suivants. Dans ces exemples, les quantités sont indiquées en pourcentage pondéral.

EXEMPLES

Exemple 1 : Mise en évidence de l'effet myorelaxant des composés selon l'invention

Le composé de formule (Ia) a été testé sur un modèle de co-culture nerfs-muscles qui permet de recréer un arc moteur en innervant des cellules musculaires striées humaines avec des explants de moelle épinière et de ganglions rachidiens d'embryons de rat.

Ce test est prédictif d'un effet anti-rides, comme cela a été mis en évidence par la Demanderesse dans le cas du diazépam, qui inhibait les contractions des fibres musculaires dans ce modèle et dont l'activité anti-rides a été démontrée in vivo.

a) Protocole

Des cellules musculaires humaines, issues de prélèvements de muscle humain de donneur sain, sont ensemencées dans des puits de 15 mm de diamètre (boîtes de culture de 24 puits). Après 10 jours de culture, ces cellules forment une monocouche et fusionnent. A ce stade, des explants de moelle épinière d'embryons de rat de 13 jours contenant le ganglion rachidien sont déposées sur la culture.

Les premières contractions des fibres musculaires sont observées après une semaine de co-culture. Après 3 semaines de co-culture, les fibres musculaires sont striées et possèdent des jonctions neuromusculaires différenciées matures.

Une fibre musculaire ayant des contractions régulières (au moins 60 contractions par minute) est alors sélectionnée dans trois puits de culture différents et le nombre de contractions est comptabilisé sur 30 secondes. Le composé testé, dilué à 1/1000 dans le DMSO, est ensuite incubé pendant 60 secondes dans ces puits, aux concentrations de 10^{-4} et 10^{-6} M. A la fin de l'incubation, le nombre de contractions est à nouveau comptabilisé sur 30 secondes.

On détermine alors le pourcentage de contractions inhibées, d'où on déduit l'IC_{50}, c'est-à-dire la concentration de produit inhibant 50% des contractions.

Pour le composé de formule (Ia), l'IC_{50} est de 10^{-6} M. L'inhibition des contractions est totale à 10^{-4} M.

Ainsi, les composés selon l'invention sont des agents myorelaxants susceptibles d'être utilisés dans le lissage des rides et ridules d'expression.

Exemple 2 : Composition cosmétique

Cette composition est préparée de manière classique pour l'homme du métier. Les quantités indiquées sont en pourcentages pondéraux.

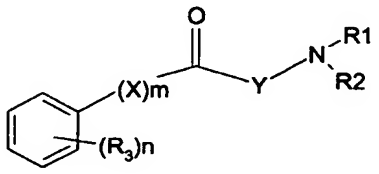
Composé de formule (Ia)	1	%
Isostéarate de propylène glycol	13	%

Polyéthylène glycol (8 OE)		5	%
Propylène glycol		3	%
Pentylène glycol		3	%
Stéarate de glycéryle et stéarate de polyéthylène glycol (100 OE)		5	%
Mono-stéarate de sorbitane oxyéthyléné (20 OE)		0,5	%
Alcool cétylique oxyéthyléné (20 OE) oxypropyléné (5 OP)		1	%
Gélifiants		0,5	%
Benzoates d'alkyle en C_{12-15}		4	%
Ethanol		3	%
Hydroxyde de sodium		0,12	%
Conservateurs		0,7	%
Eau	qsp	100	%

Ce fluide est destiné à être utilisé en applications mono- ou biquotidiennes sur le visage et le front pour atténuer les rides et ridules d'expression.

REVENDICATIONS

1. composition, adaptée à une application topique sur la peau, comprenant, dans un milieu physiologiquement acceptable, au moins un composé de formule (I) :



(I)

dans laquelle :

R_1 désigne un atome d'hydrogène ou un groupe alkyle linéaire ou ramifié, saturé ou insaturé, en C_1-C_8,

R_2 désigne un groupe alkyle linéaire ou ramifié, saturé ou insaturé, en C_1-C_{20}, éventuellement substitué,

R_3 désigne un groupe alkyle linéaire ou ramifié, saturé ou insaturé, ***(de quelle longueur ?)***, un groupe –OR, -SR, -NRR', -COOR ou $-CF_3$ ou un atome d'halogène, où R et R' désignent indépendamment un atome d'hydrogène ou un groupe alkyle en C_1-C_4, linéaire ou ramifié, ou un groupe aryle,

X est un groupe alkyle en C_1-C_9, saturé ou insaturé, éventuellement substitué,

Y est un groupe alkyle en C_1-C_{10}, saturé ou insaturé, éventuellement substitué,

les substituants de R_2, X et Y étant indépendamment choisis parmi : par un groupe alkyle, -OR, -SR, -NRR', -COOR, =O-, aryle, arylcarbonyle, alkylcarbonyle, où R et R' ont la signification donnée ci-dessus,

m est 0 ou 1,

n est compris entre 0 et 3,

ou son sel d'addition avec un acide.

2. Composition selon la revendication 1, caractérisée en ce que le sel du composé de formule (I) est obtenu par addition avec un acide inorganique choisi parmi les acides chlorhydrique, sulfurique, nitrique et phosphorique.

3. Composition selon la revendication 1, caractérisée en ce que le sel du composé de formule (I) est obtenu par addition avec un acide organique choisi parmi les acides succinique, fumarique, lactique, glycolique, citrique et tartrique.

4. Composition selon l'une quelconque des revendications 1 à 3, caractérisée en ce que m = 0 dans la formule (I).

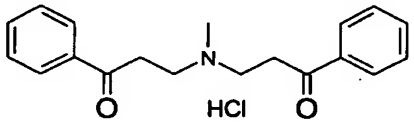
5. Composition selon l'une quelconque des revendications 1 à 4, caractérisée en ce n = 0 dans la formule (I).

6. Composition selon l'une quelconque des revendications 1 à 5, caractérisée en ce que Y est un groupe alkyle en C_1-C_3 dans la formule (I).

7. Composition selon l'une quelconque des revendications 1 à 6, caractérisée en ce que R_1 est un groupe alkyle en C_1-C_3 dans la formule (I).

8. Composition selon l'une quelconque des revendications 1 à 7, caractérisée en ce que R_2 est un groupe alkyle en C_1-C_3 substitué par un groupe arylcarbonyle dans la formule (I).

9. Composition selon l'une quelconque des revendications 1 à 8, caractérisée en ce que ledit composé de formule (I) répond à la formule (Ia) :



(Ia)

10. Composition selon l'une quelconque des revendications 1 à 9, caractérisée en ce que ledit composé de formule (I) représente de 0,1 à 2% du poids total de la composition.

11. Composition selon l'une quelconque des revendications 1 à 10, caractérisée en ce que ladite composition renferme en outre au moins un composé choisi parmi : les agents desquamants ; les agents hydratants ; les agents dépigmentants ou propigmentants ; les agents anti-glycation ; les inhibiteurs de NO-synthase ; les agents

stimulant la synthèse de macromolécules dermiques ou épidermiques et/ou empêchant leur dégradation ; les agents stimulant la prolifération des fibroblastes et/ou des kératinocytes ou stimulant la différenciation des kératinocytes ; les agents myorelaxants ; les agents tenseurs ; les agents anti-pollution et/ou anti-radicalaire ; les agents agissant sur la microcirculation ; les agents agissant sur le métabolisme énergétique des cellules ; et leurs mélanges.

12. Utilisation cosmétique d'au moins un composé de formule (I) tel que défini dans l'une quelconque des revendications 1 à 9, dans une composition adaptée à une application topique sur la peau, comme agent destiné à lisser les rides et ridules.

13. Utilisation selon la revendication 12, caractérisée en ce que lesdites rides et ridules sont des rides et ridules d'expression.

14. Procédé de traitement cosmétique d'une peau ridée, comprenant l'application topique sur ladite peau d'une composition selon l'une quelconque des revendications 1 à 11.

15. Procédé selon la revendication 14, caractérisé en ce que ladite composition est appliquée sur les zones du visage ou du front marquées par des rides et ridules d'expression et/ou sur les personnes présentant des rides et ridules d'expression.

16. Procédé selon la revendication 14 ou 15, caractérisé en ce que ladite composition est appliquée sur les rides et ridules disposées radialement autour de la bouche et/ou des yeux et/ou horizontalement sur le front et/ou situées dans l'espace inter-sourcillier.

DESCRIPTIVE ABSTRACT

Composition, in particular cosmetic, containing a secondary or tertiary carbonyl amine

This invention relates to a composition, suitable for a topical application to the skin, containing, in a physiologically acceptable medium, at least one secondary or tertiary carbonyl amine of a given formula.

It also relates to the use of such an amine in a composition suitable for a topical application to the skin, as an agent intended to smooth out wrinkles and fine lines, in particular expression wrinkles and fine lines.

This invention relates to a composition, suitable for a topical application to the skin, containing, in a physiologically acceptable medium, at least one secondary or tertiary carbonyl amine of a given formula. It also relates to the use of such an amine in a composition suitable for a topical application to the skin, as an agent intended to smooth out wrinkles and fine lines, in particular expression wrinkles and fine lines.

Women, and even men, currently have a tendency to wish to look youthful for as long as possible and consequently seek to soften the signs of aging of the skin, which are manifested especially by wrinkles and fine lines. In this respect, the media and the fashion world report about products intended to maintain for as long as possible a skin which is radiant and wrinkle-free, signs of a youthful skin, all the more so since physical appearance acts on the psyche and/or the morale.

Until now, wrinkles and fine lines were treated with cosmetic products containing active agents acting on the skin, for example by moisturizing it or by improving its cell renewal or else by promoting the synthesis, or preventing the degradation, of the elastic fibers which make up the skin tissue.

Although these treatments make it possible to act on the wrinkles and fine lines caused by chronological or intrinsic aging, as well as on those caused by photo-aging, they have no effect on expression wrinkles and fine lines, which require an intervention on the muscular contractile component of the wrinkles present in the skin.

Until now, the only means commonly used for acting on expression wrinkles has been botulinum toxin, which is injected especially into the wrinkles of the glabella, which are the wrinkles between the eyebrows (see J.D. Carruters et al., J. Dermatol. Surg. Oncol., 1992, 18, pp. 17-21).

The Applicant also has proposed various compounds capable of affording a myorelaxant effect when they are applied topically to the skin, thus making it possible to act on expression wrinkles by another route. Among these compounds there may be cited in particular the antagonists of the receptors associated with the calcium channels (FR-2-793 681) and especially manganese and its salts (FR-2 809 005) and alverine (FR-2 798 590); and agonists of the

receptors associated with the chlorine channels, including glycine (EP-0 704 210) and certain extracts of Iris pallida (FR-2 746 641).

There still is a need, however, for compounds that are effective in smoothing out or softening expression wrinkles and fine lines.

Now, the Applicant surprisingly has discovered that certain secondary or tertiary amines made it possible to satisfy this need.

Admittedly there are known from document EP-1 090 630 certain secondary and tertiary amines having the property of increasing collagen synthesis by the fibroblasts and of moisturizing the skin, useful against dry skin and atopic dermatitis, and which also show efficacy on wrinkles. The carbonyl amines cited in this document, however, do not comprise a phenyl group and are such that the carbonyl group is directly adjacent to the nitrogen atom. In addition, they have no effect on expression wrinkles and fine lines.

Moreover, there are known from document WO 93/05763 certain amines that are di- and trisubstituted with at least two chains each bearing at least one hydroxy group. These amines increase the differentiation of keratinocytes, limit the UV-induced thickening of the epidermis and are useful for preventing and treating wrinkles induced by UVB radiation. It is not suggested that these amines, different from those that are the subject of this invention in the sense that they do not comprise a carbonyl group, have any effect on expression wrinkles and fine lines.

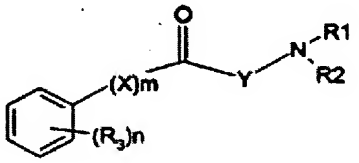
Similarly, document EP-0 691 327 discloses a very broad family of mono-, di- or trisubstituted amines described as effective for smoothing out wrinkles. The amines given as examples in this patent application, unlike the amines that are the subject of this invention, are not substituted with chains capable of comprising a carbonyl group. In addition, it is not suggested that they have any effect on expression wrinkles and fine lines.

The Applicant now has discovered that by selecting certain secondary and teretiary carbonyl amines of simple structure, it was possible to obtain cosmetic compositions effective for smoothing out expression wrinkles and fine lines.

Admittedly the use of alverine, which is a trisubstituted amine, as a myorelaxant agent intended to smooth out expression wrinkles, has been described previously by the Applicant. Unlike the compounds that are the subject of this invention, however, alverine does not contain a carbonyl group. Now, it was not obvious that the myorelaxant activity of alverine would be preserved by introduction of carbonyl groups into its molecule.

[this argument might be worth developing...]

The subject of this invention, therefore, is a composition, suitable for a topical application to the skin, comprising, in a physiologically acceptable medium, at least one compound of formula (I):



(I)

in which:

R_1 denotes a hydrogen atom or a linear or branched, saturated or unsaturated C_1-C_8 alkyl group, ***(possibly substituted?)***

R_2 denotes a linear or branched, saturated or unsaturated C_1-C_{20} alkyl group, possibly substituted,

R_3 denotes a linear or branched, saturated or unsaturated, ***(of what length?)*** alkyl group, an -OR, -SR, -NRR', -COOR or $-CF_3$ group or a halogen atom, where R and R' independently denote a hydrogen atom or a linear or branched C_1-C_4 alkyl group, or an aryl group,

X is a saturated or unsaturated C_1-C_9 alkyl group, possibly substituted,

Y is a saturated or unsaturated C_1-C_{10} alkyl group, possibly substituted,

the substituents of R_2, X and Y being independently chosen from: with an alkyl, -OR, -SR, -NRR', -COOR, =O, aryl, arylcarbonyl, alkylcarbonyl group, where R and R' have the meaning given above,

m is 0 or 1,

n is between 0 and 3,

or the addition salt thereof with an acid.

In formula (I), the alkyl groups may be chosen, depending on the case, from the groups: methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, myristyl, palmityl, stearyl and arachidyl.

For its part, the aryl group may be chosen from a benzyl group and a phenyl group.

The halogen atom may be a fluorine, chlorine, bromine or iodine atom.

As salts of the compound of formula (I), there may be cited the salts obtained by addition of the compound of formula (I) with a mineral acid, chosen in particular from hydrochloric, sulfuric, nitric, and phosphoric acids, or with an organic acid chosen in particular from succinic, fumaric, lactic, glycolic, citric and tartaric acids.

The compounds of formula (I) may be prepared in particular as described in BADOSOV, E. P. et al., Chemistry of β-Amino Ketones, VII. Synthesis of Substituted Methyl and Phenyl β-[N-methyl-N(β-acetylethyl)]aminoethyl ketones by aminomethylation of ketones with formaldehyde and the salts of methyl and phenyl β-methylaminoalkyl ketones, ***(to be completed)***, also published in Zhurnal Organicheskoi Khimii, Vol. 11, No. 5, pp. 972-977, May 1975. The synthesis of these compounds furthermore has been described in VON K. THIELE et al., Neue Piperidinderivative aus herzwirksamen –Aminoketonen, ***(to be completed)***. ***[I do not see from what works the two publications that you sent to me by fax on September 19 are taken]***

According to one preferred embodiment of the invention, the compound of formula (I) is such that at least one of the following conditions, and preferably all these conditions, are satisfied:

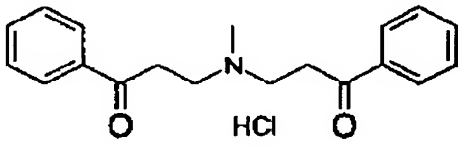
- m = 0
- n = 0

- Y is a C_1-C_3 alkyl group,
- R_1 is a C_1-C_3 alkyl group,
- R_2 is a C_1-C_3 alkyl group substituted with an arylcarbonyl group in formula (I), or the salt thereof with a mineral acid.

Even more preferably, the compound of formula (I) is such that:

- m = 0
- n = 0
- Y is an ethyl group,
- R_1 is a methyl group, and
- R_2 is an ethyl group substituted with a benzoyl group in formula (I), or the salt thereof with hydrochloric acid.

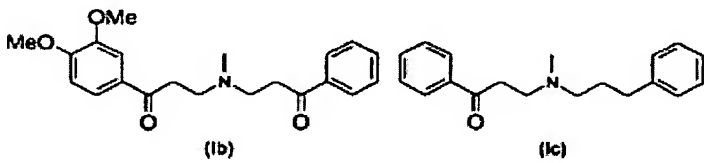
Such a compound, which corresponds to the formula (Ia) below:



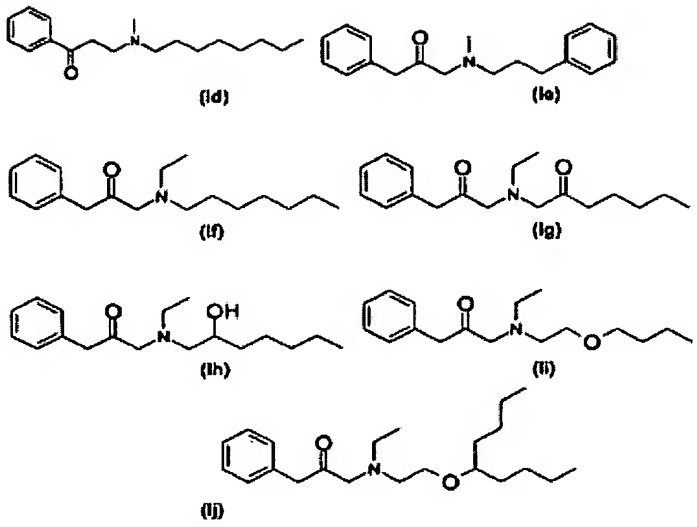
(Ia)

is available in particular from the company SALOR under the commercial reference S35,861-4. As a variant, it may be prepared by aminomethylation of acetophenone using 3-methylamino-1-phenyl-1-propanone hydrochloride (itself obtained by reacting methylamine on phenyl isopropenyl ketone) and formaldehyde, as described in the first publication indicated above.

Other examples of compounds of formula (I) useful in this invention comprise the following compounds (Ib) to (Ij):



(Ib) (Ic)



As will be shown in the Examples below, the Applicant has demonstrated a myorelaxant effect of the compounds of formula (I) according to the invention, which makes it possible to consider their use most particularly in the smoothing out of expression wrinkles and fine lines.

The quantity of compound(s) of formula (I) which may be used according to the invention is, of course, dependent on the effect sought and therefore may vary to a great extent.

To give an order of magnitude, this compound may be used in a quantity representing from 0.01% to 10% of the total weight of the composition, preferably in a quantity representing from 0.05% to 5% of the total weight of the composition, more preferably in a quantity representing from 0.1 to 2% of the total weight of the composition.

The composition according to the invention is suitable for a topical application to the skin and it therefore contains a medium that is physiologically acceptable, i.e. compatible with the skin and possibly with its integuments (eyelashes, nails, hair) and/or the mucous membranes.

This composition may be in all the galenical forms normally used in the cosmetics area, and in particular it may be in the form of an aqueous solution possibly

gelled, a dispersion of the lotion type possibly two-phase, an emulsion obtained by dispersion of a fatty phase in an aqueous phase (O/W) or conversely (W/O), or a triple emulsion (W/O/W or O/W/O) or a vesicular dispersion of ionic and/or nonionic type. These compositions are prepared according to the usual methods. A composition in the form of an oil-in-water emulsion preferably is used according to this invention.

This composition may be more or less fluid and have the appearance of a white or colored cream, a salve, a milk, a lotion, a serum, a paste, a mousse. It possibly may be applied in the form of an aerosol. It also may be in solid form, in particular in the form of a stick. It may be used as a care product and/or as a makeup product for the skin.

In known manner, the composition used according to the invention also may contain the adjuvants customary in the cosmetics area, such as hydrophilic or lipophilic gelling agents, hydrophilic or lipophilic active agents, preservatives, antioxidants, solvents, fragrances, fillers, filters, pigments, odor absorbers and coloring agents.The quantities of these various adjuvants are those ordinarily used in the area under consideration, and for example from 0.01 to 20% of the total weight of the composition. Depending on their nature, these adjuvants may be introduced into the fatty phase, into the aqueous phase or into lipid vesicles. In any event, these adjuvants, as well as the proportions thereof, shall be chosen so as not to impair the sought properties of the compounds of formula (I) according to the invention.

When the composition used according to the invention is an emulsion, the proportion of the fatty phase may range from 5 to 80% by weight and preferably from 5 to 50% by weight in relation to the total weight of the composition. The oils, emulsifiers and co-emulsifiers used in the composition in emulsion form are chosen from those ordinarily used in the area under consideration. The emulsifier and co-emulsifier are present in the composition in a proportion ranging from 0.3 to 30% by weight, and preferably from 0.5 to 20% by weight in relation to the total weight of the composition.

As oils that may be used in the invention, there may be cited mineral oils (liquid petroleum jelly), oils of plant origin (avocado oil, soybean oil), oils of animal origin (lanolin), synthetic oils (perhydrosqualene), silicone oils (cyclomethicone) and fluorous oils (perfluoropolyethers). Fatty alcohols (cetyl alcohol), fatty acids, waxes (carnauba wax, ozokerite) also may be used as fatty substances.

As emulsifiers and co-emulsifiers that may be used in the invention, there may be cited, for example, esters of fatty acid and polyethylene glycol such as PEG-100 stearate, and the esters of fatty acid and glycerol such as glyceryl stearate.

As hydrophilic gelling agents, there may be cited in particular carboxyvinyl polymers (carbomer), acrylic copolymers such as acrylate/alkylacrylate copolymers, polyacrylamides, polysaccharides, natural gums and clays, and as lipophilic gelling agents, there may be cited modified clays such as bentonites, metal salts of fatty acids, hydrophobic silica and polyethylenes.

As active agents, it will be advantageous to introduce into the composition used according to the invention at least one compound chosen from: desquamating agents; moisturizers; depigmenting or propigmenting agents; antiglycation agents; NO-synthase inhibitors; agents stimulating the synthesis of dermal or epidermal macromolecules and/or preventing their degradation; agents stimulating the proliferation of fibroblasts and/or keratinocytes or stimulating the differentiation of keratinocytes; myorelaxant agents; tensioning agents; antipollution agents and/or free-radical scavengers; agents acting on the capillary circulation; agents acting on the energy metabolism of cells; and mixtures thereof.

Examples of such additional compounds are given below.

1. Desquamating agents

By "desquamating agent" there is understood any compound capable of acting:

- either directly on desquamation by promoting exfoliation, such as β-hydroxy acids, in particular salicylic acid and its derivatives (including 5-n-octanoylsalicylic acid; α-hydroxy acids, such as glycolic, citric, lactic, tartaric, malic or mandelic acids; urea; gentisic acid; oligofucoses; cinnamic acid; extract of Saphora japonica; resveratrol;

- or on the enzymes involved in the desquamation or degradation of corneodesmosomes, glycosidases, stratum corneum chymotryptic enzyme (SCCE), or even other proteases (trypsin, chymotrypsin-like). There may be cited chelating agents for mineral salts: EDTA; N-acyl-N,N',N'-ethylenediaminetriacetic acid; aminosulfonic compounds and in particular (N-2-hydroxyethylpiperazine-N-2-ethane) sulfonic acid (HEPES); 2-oxothiazolidine-4-carboxylic acid (procysteine) derivatives; alpha amino acid derivatives of glycine type (such as described in EP-0 852 949, as well as the sodium methyl glycine diacetate sold by BASF under the trade name TRILON M); honey; sugar derivatives such as O-octanoyl-6-D-maltose and N-acetylglucosamine.

2. Moisturizer

By "moisturizer" there is understood:

- either a compound acting on the barrier function, in order to maintain moisturizing of the stratum corneum, or an occlusive compound. There may be cited ceramides, sphingoid-based compounds, lecithins, glycosphingolipids, phospholipids, cholesterol and its derivatives, phytosterols (stigmasterol, β-sitosterol, campesterol), essential fatty acids, 1-2-diacylglycerol, 4-chromanone, pentacyclic triterpenes such as ursolic acid, petroleum jelly and lanolin;

- or a compound directly increasing the water content of the stratum corneum, such as threalose and its derivatives, hyaluronic acid and its derivatives, glycerol, pentanediol, sodium pidolate, serine, xylitol, sodium lactate, polyglyceryl acrylate,

ectoin and its derivatives, chitosan, oligosaccharides and polysaccharides, cyclic carbonates, N-lauroyl pyrrolidone carboxylic acid and N-α-benzoyl-L-arginine;

- or a compound activating the sebaceous glands, such as DHEA and its derivatives and vitamin D and its derivatives.

Depigmenting or propigmenting agent

The depigmenting agents that may be incorporated into the composition according to this invention include, for example, the following compounds: kojic acid; ellagic acid; arbutin and its derivatives such as those described in applications EP-895 779 and EP-524 109; hydroquinone; aminophenol derivatives such as those described in applications WO 99/10318 and WO 99/32077, and in particular N-cholesteryloxycarbonyl-para-aminophenol and N-ethyloxycarbonyl-para-aminophenol; iminophenol derivatives, in particular those described in application WO-99/22707; L-2-oxothiazolidine-4-carboxylic acid or procysteine, as well as its salts and esters; ascorbic acid and its derivatives, especially ascorbyl glucoside; and plant extracts, in particular extracts of licorice, mulberry and skullcap, without this list's being limitative.

As a propigmenting agent, there may be cited extract of burnet (Sanguisorba officinalis) sold by the company MARUZEN, and extracts of chrysanthemum (Chrysanthemum morifolium).

4. Antiglycation agent

By "antiglycation agent" there is understood a compound preventing and/or reducing the glycation of skin proteins, in particular proteins of the dermis, such as collagen.

Examples of antiglycation agents are plant extracts of the Ericaceae family, such as an extract of blueberry (*Vaccinium angustifolium*); ergothioneine and its derivatives, and hydroxystilbenes and their derivatives, such as resveratrol and 3,3',5,5'-tetrahydroxystilbene.

5. NO-synthase inhibitor

Examples of NO-synthase inhibitors suitable for use in this invention comprise especially a plant extract of the species *Vitis vinifera* which is sold especially by the company Euromed under the name Leucocyanidines de raisins extra, or also by the company Indena under the name Leucoselect®, or finally by the company Hansen under the name Extrait de marc de raisin; a plant extract of the species *Olea europaea* which is preferably obtained from olive tree leaves and is sold especially by the company VINYALS in the form of a dry extract, or by the company Biologia & Technologia under the trade name Eurol BT; and a plant extract of the species *Gingko biloba* which is preferably a dry aqueous extract of this plant sold by the company Beaufour under the trade name Gingko biloba extrait standard.

6. Agent stimulating the synthesis of dermal or epidermal macromolecules and/or preventing their degradation

Among the active agents stimulating the macromolecules of the dermis or preventing their degradation, there may be cited those which act:

either on collagen synthesis, such as extracts of Centella asiatica; asiaticosides and derivatives; ascorbic acid or Vitamin C and its derivatives; synthetic peptides such as iamin, biopeptide CL or palmitoyloligopeptide sold by the company SEDERMA; peptides extracted from plants, such as the soybean hydrolysate sold by the company COLETICA under the trade name Phytokine®; and plant hormones such as auxines;

- or on elastin synthesis, such as the extract of Saccharomyces Cerivisiae sold by the company LSN under the trade name Cytovitin®; and the extract of the alga Macrocystis pyrifera sold by the company SECMA under the trade name Kelpadelie®;

- or on glycosaminoglycan synthesis, such as the product of fermentation of milk with Lactobacillus vulgaris, sold by the company BROOKS under the trade name

Biomin yogourth®; the extract of the brown alga Padina pavonica sold by the company ALBAN MULLER under the trade name HSP3®; and the extract of Saccharomyces cerevisiae available especially from the company SILAB under the trade name Firmalift® or from the company LSN under the trade name Cytovitin®;

- or on fibronectin synthesis, such as the extract of zooplankton Salina sold by the company SEPORGA under the trade name GP4G®; the yeast extract available especially from the company ALBAN MULLER under the trade name Drieline®; and the palmitoyl pentapeptide sold by the company SEDERMA under the trade name Matrixil®;

- or on metalloproteinase (MMP) inhibition, such as, more particularly, MMP 1, 2, 3, 9. There may be cited: retinoids and derivatives, oligopeptides and lipopeptides, lipoamino acids, the malt extract sold by the company COLETICA under the trade name Collalift®; extracts of blueberry or of rosemary; lycopene; isoflavones, their derivatives or plant extracts containing them, in particular extracts of soybean (sold, for example, by the company ICHIMARU PHARCOS under the trade name Flavosterone SB®), of red clover, of flax, of kakkon or of sage;

- or on the inhibition of serine proteases such as leukocyte elastase or cathepsin G. There may be cited: the peptide extract of Leguminosa seeds (Pisum sativum) sold by the company LSN under the trade name Parelastyl®; heparinoids; and pseudodipeptides.

Among the active agents stimulating epidermal macromolecules, such as fillagrin and keratins, there may be cited especially the extract of lupin sold by the company SILAB under the trade name Structurine®; the extract of beech Fagus sylvatica buds sold by the company GATTEFOSSE under the trade name Gatuline®; and the extract of zooplankton Salina sold by the company SEPORGA under the trade name GP4G®.

7. Agent stimulating the proliferation of fibroblasts or keratinocytes and/or keratinocyte differentiation

The agents stimulating the proliferation of fibroblasts that may be used in the composition according to the invention may be chosen, for example, from plant proteins or polypeptides, extracts, especially of soybean (for example an extract of soybean sold by the company LSN under the name Eleseryl SH-VEG 8® or sold by the company SILAB under the trade name Raffermine®); and plant hormones such as giberrellins and cytokinins.

The agents stimulating keratinocyte proliferation that may be used in the composition according to the invention comprise especially retinoids such as retinol and its esters, including retinyl palmitate; phloroglucinol; extracts of nut cakes sold by the company GATTEFOSSE; and extracts of Solanum tuberosum sold by the company SEDERMA.

The agents stimulating keratinocyte differentiation comprise, for example, minerals such as calcium; the extract of lupin sold by the company SILAB under the trade name Photopreventine®; sodium beta-sitosteryl sulfate sold by the company SEPORGA under the trade name Phytocohesine®; and the extract of corn sold by the company SOLABIA under the trade name Phytovityl®.

8. Myorelaxant agent

In addition to the compound of formula (I) described above, the composition according to the invention may comprise other myorelaxant agents, among which there may be cited in particular alverine and its salts, especially alverine citrate, manganese gluconate, sapogenins such as diosgenin and the natural extracts containing them (such as extracts of Wild Yam), as well as hexapeptide argireline R sold by the company LIPOTEC.

9. Tensioning agent

By "tensioning agent" there is understood a compound capable of exerting tension on the skin, which has the effect of temporarily softening irregularities, such as wrinkles and fine lines, on the surface of the skin.

Among the tensioning agents that may be used in the composition according to this invention, there may be cited especially:

(1) synthetic polymers, such as polyurethane latices or acrylic-silicone latices, in particular those described in patent application EP-1038519, such as a propylthio(polymethyl acrylate), propylthio(polymethyl methacrylate) and propylthio(polymethacrylic acid) grafted polydimethylsiloxane, or else a propylthio (polyisobutyl methacrylate) and propylthio(polymethacrylic acid) grafted polydimethylsiloxane. Such grafted silicone polymers are sold especially by the company 3M under the trade names VS 80, VS 70 or LO21,
(2) polymers of natural origin, especially (a) polyholosides, for example (i) in the form of starch derived especially from rice, corn, potato, cassava, pea, *triticum aestivum* wheat, oat, etc.... or (ii) in the form of carrageenans, alginates, agars, gelans, cellulose-based polymers and pectins, advantageously in an aqueous dispersion of gel microparticles, and (b) latices consisting of shellac resin, sandarac gum, dammar resins, elemi gums, copal resins and cellulose-based derivatives, and mixtures thereof,
(3) plant proteins and protein hydrolysates, in particular from corn, rye, *triticum aestivum* wheat, buckwheat, sesame, spelt, pea, bean, lentil, soybean and lupin,
(3) mixed silicates, especially phyllosilicates and in particular Laponites.
(4) wax microparticles chosen for example, from Carnauba, Candelilla and Alfalfa waxes,
(5) colloidal particles of mineral filler with a number-average diameter between 0.1 and 100 nm, preferably between 3 and 30 nm, and chosen, for example, from: silica, cerium oxide, zirconium oxide, alumina, calcium carbonate, barium sulfate, calcium sulfate, zinc oxide and titanium dioxide.

10. Anti-pollution agent or free-radical scavenger

By the term "anti-pollution agent" there is understood any compound capable of trapping ozone, monocyclic or polycyclic aromatic compounds such as benzopyrene and/or heavy metals such as cobalt, mercury, cadmium and/or nickel. By "free-radical scavenger" there is understood any compound capable of trapping free radicals.

As ozone-trapping agents that may be used in the composition according to the invention, there may be cited in particular vitamin C and its derivatives including ascorbyl glucoside; phenols and polyphenols, in particular tannins, ellagic acid and tannic acid; epigallocatechin and natural extracts containing it; extracts of olive tree leaf; extracts of tea, in particular of green tea; anthocyans; extracts of rosemary; phenol acids, in particular chlorogenic acid; stilbenes, in particular resveratrol; sulfur-containing amino acid derivatives, in particular S-carboxymethylcysteine; ergothioneine; N-acetyl-cysteine; chelating agents such as N,N'-bis-(3,4,5-trimethoxybenzyl)ethylenediamine or one of its salts, metal complexes or esters; carotenoids such as crocetin; and various starting materials such as the mixture of arginine, histidine ribonucleate, mannitol, adenosine triphosphate, pyridoxine, phenylalanine, tyrosine and hydrolyzed RNA, sold by the Laboratoires Serobiologiques under the trade name CPP LS 2633-12F®, the water-soluble fraction of corn sold by the company SOLABIA under the trade name Phytovityl®, the mixture of extract of fumitory and of extract of lemon sold under the name Unicotrozon C-49® by the company Induchem, and the mixture of extracts of ginseng, of apple, of peach, of wheat and of barley, sold by the company PROVITAL under the trade name Pronalen Bioprotect®.

As agents for trapping monocyclic or polycyclic aromatic compounds which may be used in the composition according to the invention, there may be cited in particular tannins such as ellagic acid; indole derivatives, in particular 3-indolecarbinol; extracts of tea, in particular of green tea, extracts of water hyacinth or Eichornia crassipes; and the water-soluble fraction of corn sold by the company SOLABIA under the trade name Phytovityl®.

Finally, as heavy-metal-trapping agents that may be used in the composition according to the invention, there may be cited in particular chelating agents such as EDTA, the pentasodium salt of ethylenediaminetetramethylenephosphonic acid, and N,N'-bis-(3,4,5-trimethoxybenzyl)ethylenediamine or one of the salts,

metal complexes or esters thereof; phytic acid; chitosan derivatives; extracts of tea, in particular of green tea; tannins such as ellegic acid; sulfur-containing amino acids such as cysteine; extracts of water hyacinth (Eichornia crassipes); and the water soluble fraction of corn sold by the company SOLABIA under the trade name Phytovityl®.

The free-radical savengers that may be used in the composition according to the invention comprise, besides certain anti-pollution agents mentioned previously, vitamin E and its derivatives such as tocopheryl acetate; bioflavonoids; coenzyme Q10 or ubiquinone; certain enzymes, such as catalase, superoxide dismutase, lactoperoxidase, glutathione peroxidase and quinone reductases; glutathione; benzylidenecamphor; benzylcyclanones; substituted napthalenones; pidolates; phytanetriol; gamma-oryzanol; lignans; and melatonin.

11. Agents acting on the capillary circulation

The active agents acting on the capillary circulation (vasoprotective or vasodilating agents) are found especially among flavonoids, ruscogenins, esculosides, escin extracted from common horse chestnut, nicotinates, heperidine methyl chalcone, essential oils of lavender or of rosemary, extracts of *Ammi Visnaga.*

12. Agents acting on the energy metabolism of cells

By this expression there is understood active agents acting on the energy metabolism of the skin, such as, for example, and in non-limitative manner, ATP synthesis, as well as those involved in the respiratory chain of the cells or in the energy reserves. There may be cited in this respect Coenzyme Q10 (ubiquinone), cytochrome C, creatine or also phosphocreatine.

As indicated previously, the composition according to the invention also may contain UVA and/or UVB screening agents in the form of organic or mineral compounds, the latter possibly being coated to make them hydrophobic.

The organic screening agents may be chosen especially from: anthranilates, in particular menthyl anthranilate; benzophenones, in particular benzophenone-1,

benzophenone-3, benzophenone-5, benzophenone-6, benzophenone-8, benzophenone-9, benzophenone-12, and preferably benzophenone-3 (oxybenzone) or benzophenone-4 (Uvinul MS40 available from BASF); benzylidenecamphors, in particular 3-benzylidenecamphor, benzylidenecamphorsulfonic acid, camphor benzalkonium methosulfate, polyacrylamido methylbenzylidenecamphor, terephthalylidenedicamphorsulfonic acid, and preferably 4-methylbenzylidenecamphor (Eusolex 6300 available from Merck); benzimidazoles, in particular benzimidazilate (Neo Heliopan AP available from Haarmann & Reimer), or phenylbenzimidazolesulfonic acid (Eusolex 232 available from Merck); benzotriazoles, in particular drometrizole trisiloxane, or methylenebis-benzotriazolyltetramethylbutylphenol (Tinosorb M available from Ciba); cinnamates, in particular cinoxate, DEA methoxycinnamate, diisopropyl methylcinnamate, glyceryl ethylhexanoate dimethoxycinnamate, isopropyl methoxycinnamate, isoamyl cinnamate, and preferably ethocrylene (Uvinul N35 available from B.A.S.F.), octyl methoxycinnamate (Parsol MCX available from Hoffmann La Roche), or octocrylene (Uvinul 539 available from B.A.S.F.); dibenzoylmethanes, in particular butylmethoxydibenzoylmethane (Parsol 1789); imidazolines, in particular ethylhexyl dimethoxybenzylidene dioxoimidazoline; PABAs, in particular ethyl dihydroxypropyl PABA, ethylhexyldimethyl PABA, glyceryl PABA, PABA, PEG-25 PABA, and preferably diethylhexylbutamidotriazone (Uvasorb HEB available from 3V Sigma), ethylhexyltriazone (Uvinul T150 available from B.A.S.F.) or ethyl PABA (benzocaine); salicylates, in particular dipropylene glycol salicylate, ethylhexyl salicylate, homosalate or TEA salicylate; triazines, in particular anisotriazine (Tinosorb S available from Ciba); drometrizole trisiloxane.

The mineral screening agents preferably consist of zinc oxide and/or titanium dioxide, preferably of nanometric size, possibly coated with alumina and/or stearic acid.

The invention therefore also has as a subject the cosmetic use of at least one compound of formula (I) as defined above, in a composition suitable for a topical application to the skin, as an agent intended to smooth out wrinkles and fine lines, in particular expression wrinkles and fine lines.

It likewise has as a subject a method for cosmetic treatment of a wrinkled skin, comprising the topical application to said skin of a composition such as defined previously.

The composition according to the invention advantageously is intended to be applied to the areas of the face or forehead marked with expression wrinkles or fine lines, and/or to individuals having expression wrinkles and fine lines.

The wrinkles and fine lines concerned preferably are those lying radially around the mouth and/or the eyes, in particular the crow's feet wrinkles, and/or lying on the forehead, in particular the so-called lion wrinkle, located in the glabella, between the eyebrows, and/or lying horizontally on the forehead.

The invention now will be illustrated with the following non-limitative examples. In these examples, the quantities are indicated as percentage by weight.

EXAMPLES

Example 1: Demonstration of the myorelaxant effect of the compounds according to the invention

The compound of formula (Ia) was tested on a nerve-muscle co-culture model that makes it possible to recreate a motor arc by innervating human striated muscle cells with explants of spinal cord and spinal-column ganglia of rat embryos.

This test is predicative of an anti-wrinkle effect, as was demonstrated by the Applicant in the case of diazepam, which inhibited contractions of the muscle fibers in this model and the anti-wrinkle activity of which was demonstrated in vivo.

a) Protocol

Human muscle cells, derived from samples of human muscle from a healthy donor, are cultured in wells 15 mm in diameter (24-well culture dishes). After 10

days of culture, these cells form a monolayer and merge. At this stage, explants of spinal cord from 13-day rat embryos containing spinal-column ganglia are deposited onto the culture.

The first contractions of muscle fibers are observed after one week of co-culture. After 3 weeks of co-culture, the muscle fibers are striated and possess mature differentiated neuromuscular junctions.

A muscle fiber having regular contractions (at least 60 contractions per minute) then is selected in three different culture wells and the number of contractions is counted over 30 seconds. The compound tested, diluted to 1/1000 in DMSO, then is incubated for 60 seconds in these wells, at concentrations of 10^{-4} and 10^{-6} M. At the end of incubation, the number of contractions is counted again over 30 seconds.

There then is determined the percentage of inhibited contractions, wherefrom there is deduced the IC_{50}, that is, the product concentration inhibiting 50% of the contractions.

For the compound of formula (Ia), the IC_{50} is 10^{-6} M. The inhibition of contractions is total at 10^{-4} M.

Thus, the compounds according to the invention are myorelaxant agents capable of being used in the smoothing out of expression wrinkles and fine lines.

Example 2: Cosmetic composition

This composition is prepared in a manner conventional for the individual skilled in the art. The quantities indicated are in percentages by weight.

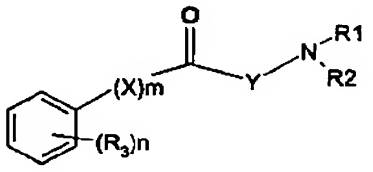
Compound of formula (Ia)	1 %
Propylene glycol isostearate	13%

Polyethylene glycol (8 EO)		5%
Propylene glycol		3%
Pentylene glycol		3%
Glyceryl stearate and polyethylene glycol stearate (100 EO)		5%
Oxyethylenated sorbitan monostearate (20 EO)		0.5%
Oxyethylenated (20 EO) oxypropylenated (5 PO) cetyl alcohol		1%
Gelling agents		0.5%
C_{12-15} alkyl benzoates		4%
Ethanol		3%
Sodium hydroxide		0.12%
Preservatives		0.7%
Water	qsp	100%

This fluid is intended to be used in applications once or twice a day to the face and the forehead to attenuate expression wrinkles and fine lines.

CLAIMS

1. A composition, suitable for a topical application to the skin, comprising, in a physiologically acceptable medium, at least one compound of formula (I):



(I)

in which:

R_1 denotes a hydrogen atom or a linear or branched, saturated or unsaturated C_1-C_8 alkyl group,

R_2 denotes a linear or branched, saturated or unsaturated C_1-C_{20} alkyl group, possibly substituted,

R_3 denotes a linear or branched, saturated or unsaturated, ***(of what length?)*** alkyl group, an –OR, -SR, -NRR', -COOR or -CF_3 group or a halogen atom, where R and R' independently denote a hydrogen atom or a linear or branched C_1-C_4 alkyl group, or an aryl group,

X is a saturated or unsaturated C_1-C_9 alkyl group, possibly substituted,

Y is a saturated or unsaturated C_1-C_{10} alkyl group, possibly substituted,

the substituents of R_2, X and Y being chosen independently from: with an alkyl, -OR, -SR, -NRR', -COOR, =O-, aryl, arylcarbonyl, alkylcarbonyl group, where R and R' have the meaning given above,

m is 0 or 1,

n is between 0 and 3,

or the addition salt thereof with an acid.

2. A composition according to claim 1, characterized in that the salt of the compound of formula (I) is obtained by addition with a mineral acid chosen from hydrochloric, sulfuric, nitric and phosphoric acids.

3. A composition according to claim 1, characterized in that the salt of the compound of formula (1) is obtained by addition with an organic acid chosen from succinic, fumaric, lactic, glycolic, citric and tartaric acids.

4. A composition according to any one of claims 1 to 3, characterized in that m = 0 in formula (I).

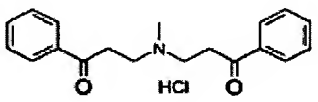
5. A composition according to any one of claims 1 to 4, characterized in that n = 0 in formula (I).

6. A composition according to any one of claims 1 to 5, characterized in that Y is a C_1-C_3 alkyl group in formula (I).

7. A composition according to any one of claims 1 to 6, characterized in that R_1 is a C_1-C_3 alkyl group in formula (I).

8. A composition according to any one of claims 1 to 7, characterized in that R_2 is a C_1-C_3 alkyl group substituted with an arylcarbonyl group in formula (I).

9. A composition according to any one of claims 1 to 8, characterized in that the said compound of formula (I) corresponds to formula (Ia):



(Ia)

10. A composition according to any one of claims 1 to 9, characterized in that the said compound of formula (I) represents from 0.1 to 2% of the total weight of the composition.

11. A composition according to any one of claims 1 to 10, characterized in that the said composition further comprises at least one compound chosen from: desquamating agents; moisturizers; depigmenting or propigmenting agents; antiglycation agents; NO-synthase inhibitors; agents stimulating the synthesis of dermal or epidermal macromolecules and/or preventing their degradation; agents

stimulating the proliferation of fibroblasts and/or keratinocytes or stimulating the differentiation of keratinocytes; myorelaxant agents; tensioning agents; antipollution agents and/or free-radical scavengers; agents acting on the capillary circulation; agents acting on the energy metabolism of cells; and mixtures thereof.

12. A cosmetic use of at least one compound of formula (I) such as defined in any one of claims 1 to 9, in a composition suitable for a topical application to the skin, as an agent intended to smooth out wrinkles and fine lines.

13. A use according to claim 12, characterized in that the said wrinkles and fine lines are expression wrinkles and fine lines.

14. A method for cosmetic treatment of a wrinkled skin, comprising the topical application to the said skin of a composition according to any one of claims 1 to 11.

15. A method according to claim 14, characterized in that the said composition is applied to the areas of the face or the forehead marked with expression wrinkles and fine lines and/or to individuals having expression wrinkles and fine lines.

16. A method according to claim 14 or 15, characterized in that the said composition is applied to wrinkles and fine lines lying radically around the mouth and/or the eyes and/or horizontally on the forehead and/or located between the eyebrows.

AFFIRMED in part and REVERSED in part.

BURROUGHS WELLCOME CO., Plaintiff–Appellee,

v.

BARR LABORATORIES, INC., Defendant–Appellant,

and

Novopharm, Inc. and Novopharm, Ltd., Defendants–Appellants.

Nos. 93–1503 to 93–1505.

United States Court of Appeals, Federal Circuit.

Nov. 22, 1994.

Rehearing Denied Dec. 15, 1994.

Pharmaceutical manufacturer brought patent infringement action with respect to six patents covering various methods of using azidothymidine (AZT) in treatment of persons affected with human immunodeficiency virus (HIV). The United States District Court for the Eastern District of North Carolina, Malcom J. Howard, J., entered judgment as matter of law in favor of manufacturer, 828 F.Supp. 1208, and alleged infringers appealed. The Court of Appeals, Mayer, Circuit Judge, held that: (1) National Institute of Health (NIH) scientists who confirmed that AZT was effective against HIV at request of pharmaceutical manufacturer were not coinventors with regard to patents encompassing compositions of methods of using AZT to treat acquired immunodeficiency syndrome (AIDS), but (2) issue of whether NIH scientists were coinventors with regard to patent for using AZT to increase number of T-lymphocytes in humans infected with HIV was question of fact for jury.

Affirmed in part, vacated in part and remanded.

Lourie, Circuit Judge, concurred in part and dissented in part.

1. Patents ⇐92

National Institute of Health (NIH) scientists who confirmed that azidothymidine (AZT) was effective against the human immunodeficiency virus (HIV) at request of pharmaceutical manufacturer were not coinventors with regard to manufacturer's patents encompassing compositions and methods of using AZT to treat acquired immunodeficiency syndrome (AIDS); draft British patent application showed that manufacturer's inventors had already conceived of invention at time of NIH experiments. 35 U.S.C.A. § 116.

2. Federal Courts ⇐776

District court's grant of judgment as matter of law is subject to de novo review. Fed.Rules Civ.Proc.Rule 50(a), 28 U.S.C.A.

3. Federal Courts ⇐764, 798

In reviewing grant of judgment as matter of law, Court of Appeals must apply same standard as did district court, examining record in light most favorable to nonmovant and drawing inferences in that party's favor; Court of Appeals may affirm only if judgment entered was only one possible under the controlling law. Fed.Rules Civ.Proc. Rule 50(a), 28 U.S.C.A.

4. Patents ⇐92

"Joint invention" is product of collaboration between two or more persons working together to solve problem addressed. 35 U.S.C.A. § 116.

See publication Words and Phrases for other judicial constructions and definitions.

5. Patents ⇐90(1)

Conception is touchstone of inventorship, the completion of mental part of invention.

6. Patents ⇐90(1)

Conception of invention is complete only when idea is so clearly defined in inventor's mind that only ordinary skill would be necessary to reduce invention to practice, without extensive research or experimentation.

7. Patents ⇐90(1)

Tests for conception of invention is whether inventor had idea that was definite and permanent enough that one skilled in art could understand invention; inventor must prove his or her conception by corroborating evidence, preferably by showing contemporaneous disclosure.

8. Patents ⇐90(1)

Idea is definite and permanent, as required for conception of invention, when inventor has specific, settled idea, particular solution to problem at hand, not just general goal or research plan he or she hopes to pursue.

9. Patents ⇐90(1)

Inventor need not know that his or her invention will work for conception to be complete.

10. Patents ⇐90(1)

Inventor need only show that he or she had idea for conception to be complete; discovery that invention actually works is part of its reduction to practice.

11. Patents ⇐90(1)

Inventor's belief that his or her invention will work or his or her reasons for choosing particular approach are irrelevant to conception of invention.

12. Patents ⇐90(1)

Enablement and conception are distinct issues, and one need not necessarily meet enablement standard to prove conception. 35 U.S.C.A. § 112.

13. Patents ⇐314(5)

Issue of whether National Institute of Health (NIH) scientists were coinventors with regard to pharmaceutical manufacturer's patent for using azidothymidine (AZT) to increase number of T-lymphocytes in humans infected with human immunodeficiency virus (HIV) was question of fact for jury; NIH scientists reported that AZT resulted in increase in T-lymphocytes when testing AZT for manufacturer, and evidence conflicted as to whether those skilled in the art would have expected increasing T-lymphocyte function to accompany inhibition of HIV. 35 U.S.C.A. § 116.

14. Patents ⇐90(1)

For conception of invention, Court of Appeals looks not to whether one skilled in the art could have thought of invention, but whether alleged inventors actually had in their minds required method and permanent idea.

E. Anthony Figg, Rothwell, Figg, Ernst & Kurz, Washington, DC, argued for plaintiff-appellee. With him on the brief were Steven Lieberman and Joseph A. Hynds. Of counsel was Mark A. Ash. Also on the brief were Thomas F. Curnin, Laura Mezey, Daniel L. Cantor and Michael B. Weiss, Cahill, Gordon & Reindel, New York City. Of counsel were Paul A. Holcombe, Jr. and Susan S. Dunn, Burroughs Wellcome Co., Research Triangle Park, NC.

Dan K. Webb, Winston & Strawn, Chicago, IL, argued for defendant-appellant. With him on the brief were Eric L. Hirschhorn, George C. Lombardi, James F. Hurst and Monique M. Vasilchik. Also on the brief were Myron Cohen and Michael C. Stuart, Cohen, Pontani, Lieberman & Pavane, New York City. Robert F. Green, Leydig, Voit & Mayer, Ltd., Chicago, IL, argued for defendants-appellants. With him on the brief were Bruce M. Gagala, Richard M. Johnson and Regina M. Anderson. Of counsel was Jeffrey S. Ward, Chicago, IL.

Before MAYER, LOURIE, and SCHALL, Circuit Judges.

MAYER, Circuit Judge.

Barr Laboratories, Inc., Novopharm, Inc., and Novopharm, Ltd., appeal the order of the United States District Court for the Eastern District of North Carolina, *Burroughs Wellcome Co. v. Barr Lab., Inc.*, 828 F.Supp. 1208 (E.D.N.C.1993), granting the motion of Burroughs Wellcome Co. for judgment as a matter of law that six United States patents were not invalid and were infringed. We affirm in part, vacate in part, and remand.

Background

Burroughs Wellcome Co. is the owner of six United States patents that cover various preparations of 3'–azidothymidine (AZT) and methods for using that drug in the treatment of persons infected with the human immunodeficiency virus (HIV).[1] Each of these patents names the same five inventors—Janet Rideout, David Barry, Sandra Lehrman, Martha St. Clair, and Phillip Furman (Burroughs Wellcome inventors)—all of whom were employed by Burroughs Wellcome at the time the inventions were alleged to have been conceived. The defendants-appellants concede that all five are properly named as inventors on the patents.

Burroughs Wellcome's patents arise from the same parent application filed on September 17, 1985.[2] Five of the patents relate to the use of AZT to treat patients infected with HIV or who have acquired immunodeficiency syndrome (AIDS).[3] The other patent, the '750 patent, covers a method of using AZT to increase the T-lymphocyte count of persons infected with HIV.[4]

In the early 1980s, scientists began to see patients with symptoms of an unknown disease of the immune system, now known as AIDS. The disease attacks and destroys certain white blood cells known as CD4 T-lymphocytes or T-cells, which form an important component of the body's immune system. The level of destruction eventually becomes so great that the immune system is no longer able to mount an effective response to infections that pose little threat to a healthy person.

In mid–1984, scientists discovered that AIDS was caused by a retrovirus, known as HTLV III or, more commonly today, HIV. After the identification of HIV, Burroughs Wellcome began to search for a cure, screening compounds for antiretroviral activity using two murine (or mouse) retroviruses, the Friend leukemia virus and the Harvey sarcoma virus.

At about this time, scientists at the National Institutes of Health (NIH), led by Samuel Broder, were looking for effective AIDS therapies as well. Unlike Burroughs Wellcome, Broder and his colleagues used live HIV, and were able to develop a test that could demonstrate a compound's effectiveness against HIV in humans using a unique line of T-cell clones (the ATH8 cell line). The NIH scientists began to seek compounds from private pharmaceutical companies for screening in their cell line. After Burroughs Wellcome contacted Broder in the fall of

1. Although two of the patents claim pharmaceutical compositions of AZT, not methods of treatment per se, the parties treat all of the patents as covering the particular use of AZT as a treatment for AIDS and its symptoms. The district court adopted this interpretation and applied the patents as though all claimed methods of treatment; no party argues for another interpretation, so we do the same.

2. The following patents are at issue: U.S. Patent No. 4,724,232 (the '232 patent), filed September 17, 1985, issued February 9, 1988; No. 4,828,838 (the '838 patent), filed October 21, 1987, issued May 9, 1989; No. 4,833,130 (the '130 patent), filed October 20, 1987, issued May 23, 1989; No. 4,837,208 (the '208 patent), filed October 20, 1987, issued June 6, 1989; No. 4,818,538 (the '538 patent), filed October 21, 1987, issued April 4, 1989; and No. 4,818,750 (the '750 patent), filed October 20, 1987, issued April 4, 1989.

3. Claim 1 of the '232 patent covers "[a] method of treating a human having acquired immunodeficiency syndrome comprising the oral administration of an effective acquired immunodeficiency syndrome treatment amount of 3'–azido–3'–deoxythymidine to said human."

Claim 1 of the '838 patent covers "[a] pharmaceutical preparation comprising a capsule containing 5 to 500 mg of 3'–azido–3'–deoxythymidine."

Claim 1 of the '130 patent covers "[a] method of treating a human having an HTLV III virus infection comprising administering to said human an effective HTLV III virus treatment amount of 3'–azido–3'–deoxythymidine."

Claim 1 of the '208 patent covers "[a] method of treating a human having antibodies to the HTLV III virus which comprises administering to said human an effective HTLV III treatment amount of 3'–azido–3'–deoxythymidine."

Claim 1 of the '538 patent covers "[a] sealed container including a pharmaceutical composition in unit dosage form comprising 5 to 500 mg of 3'–azido–3'–deoxythymidine together with a pharmaceutically acceptable solid carrier."

4. Claim 1 of the '750 patent covers "[a] method of increasing the number of T-lymphocytes in a human infected with the HTLV III virus comprising administering to said human an effective amount of 3'–azido–3'–deoxythymidine or a pharmaceutically acceptable alkali metal, alkaline earth or ammonium salt thereof."

1984, he agreed to accept compounds from Burroughs Wellcome under code for testing against live HIV.

Burroughs Wellcome's Rideout selected AZT and a number of other compounds for testing in the murine screens on October 29, 1984. The tests, performed at Burroughs Wellcome facilities by St. Clair, showed that AZT had significant activity against both murine retroviruses at low concentrations. In light of these positive results, the Burroughs Wellcome inventors met on December 5, 1984, to discuss patenting the use of AZT in the treatment of AIDS. Burroughs Wellcome's patent committee thereafter recommended that the company prepare a patent application for future filing. By February 6, 1985, the company had prepared a draft application for filing in the United Kingdom. The draft disclosed using AZT to treat patients infected with HIV, and set out various pharmaceutical formulations of the compound in an effective dosage range to treat HIV infection.

Two days earlier, on February 4, 1985, Burroughs Wellcome had sent a sample of AZT, identified only as Compound S, to Broder at NIH. In an accompanying letter, Lehrman told Broder of the results of the murine retrovirus tests and asked that he screen the compound for activity against HIV in the ATH8 cell line. Another NIH scientist, Hiroaka Mitsuya, performed the test in mid-February 1985, and found that Compound S was active against HIV. Broder informed Lehrman of the results by telephone on February 20, 1985. Burroughs Wellcome filed its patent application in the United Kingdom on March 16, 1985.

After Burroughs Wellcome learned that AZT was active against HIV, it began the process of obtaining Food and Drug Administration (FDA) approval for AZT as an AIDS therapy. As a part of the clinical trials leading to FDA approval, Broder and another NIH scientist, Robert Yarchoan, conducted a Phase I human patient study which showed that treatment with AZT could result in an increase in the patient's T-cell count. Broder reported this result to Lehrman on July 23, 1985. In 1987, the FDA approved AZT for marketing by Burroughs Wellcome; Burroughs Wellcome markets the drug for treatment of HIV infection under the trademark Retrovir.

On March 19, 1991, Barr Laboratories, Inc. (Barr) sought FDA approval to manufacture and market a generic version of AZT by filing an Abbreviated New Drug Application (ANDA) pursuant to 21 U.S.C. § 355(j) (1988). As part of the process, Barr certified to the FDA that Burroughs Wellcome's patents were invalid or were not infringed by the product described in its ANDA. After Barr informed Burroughs Wellcome of its action, Burroughs Wellcome commenced this case for patent infringement against Barr on May 14, 1991, alleging technical infringement of its patents under 35 U.S.C. § 271(e)(2)(A) (1988).

Barr filed a counterclaim under 35 U.S.C. § 256 (1988) seeking correction of the patents to list Broder and Mitsuya as coinventors. Barr admitted that its AZT product would infringe the patents, but contended that it did not because Barr had obtained a license to manufacture and sell AZT from the government, which should be deemed the owner of the interest of coinventors Broder and Mitsuya in the AZT patents. Burroughs Wellcome denied that Broder and Mitsuya were coinventors and also responded that the assertion of any rights of Broder, Mitsuya, or the government in the patents was barred by laches, estoppel, and waiver.

Thereafter, Novopharm, Ltd. filed an ANDA of its own, seeking approval to manufacture and market its generic version of AZT. Burroughs Wellcome filed infringement suits against Novopharm, Ltd. and its American subsidiary Novopharm, Inc., which were consolidated with the suit against Barr.[5] Like Barr, Novopharm, Ltd. admitted that its AZT product would infringe the claims of the six patents, but for the failure of Burroughs Wellcome to name the NIH scientists as coinventors of the subject matter of the patents. Although Novopharm, Inc. agreed

5. Novopharm, Inc. and Novopharm, Ltd. are jointly represented by counsel and make many of the same arguments on appeal. Except where it is more appropriate to refer to them individually, we will refer to them together as Novopharm.

to be bound by any injunction issued against its parent, it argued that it had not infringed the patents because it had not filed an ANDA and had no AZT product of its own.[6] Novopharm contended that Broder and Mitsuya should have been named as inventors on five of the patents, and contended that Broder and Yarchoan were coinventors of the '750 patent. It maintained that the patents were invalid because of the alleged nonjoinder, and because Burroughs Wellcome had omitted the coinventors with deceptive intent, the patents were unenforceable for inequitable conduct.

After more than three weeks of trial, while Burroughs Wellcome was still in the process of presenting its case, the district court granted Burroughs Wellcome's motion for judgment as a matter of law against all of the defendants, concluding that the Burroughs Wellcome inventors had conceived of the subject matter of the inventions at some time before February 6, 1985, without the assistance of Broder, Mitsuya, or Yarchoan. The court rejected the arguments of Barr and Novopharm that they should be allowed to present evidence that the Burroughs Wellcome inventors had no reasonable belief that the inventions would actually work—that AZT was in fact active against HIV—until they were told the results of the NIH testing.

The court also rejected Novopharm's argument that the Burroughs Wellcome inventors had not conceived the invention of the '750 patent—the use of AZT to increase a patient's T-cell count—before July 23, 1985, when Broder reported the results of the NIH patient study to Lehrman. The court concluded that the increase in T-cell count was an obvious phenomenon known to the inventors that would result from administration of AZT. And the district court denied Barr's renewed motion for partial summary judgment on Burroughs Wellcome's equitable defenses to its counterclaim for correction of the patents under section 256.

6. Burroughs Wellcome alleges that Novopharm, Inc. is liable for the infringement by Novopharm, Ltd. on grounds that it participated in or induced Novopharm, Ltd.'s infringing activities. But Burroughs Wellcome had the burden of proving infringement by Novopharm, Inc. and on the record before us there is simply no evidence to support a conclusion on this factual question. The judgment against Novopharm, Inc. is vacated.

Discussion

[1] The arguments of both Barr and Novopharm are directed to when the inventors conceived the invention. Burroughs Wellcome says it was before they learned the results of the NIH tests; Barr and Novopharm say that confirmation of the inventions' operability, which came from the NIH tests, was an essential part of the inventive process. If Burroughs Wellcome is right, then the patents name the proper inventors, they are not invalid, and the appellants are liable for infringement. If Barr and Novopharm are correct, then Broder, Mitsuya, and Yarchoan should have been named as joint inventors and the resolution of Burroughs Wellcome's infringement suits is premature.

[2, 3] The district court's grant of judgment as a matter of law under Rule 50(a) is subject to de novo review. *Read Corp. v. Portec, Inc.*, 970 F.2d 816, 821, 23 USPQ2d 1426, 1431 (Fed.Cir.1992). We must apply the same standard as did that court, examining the record in the light most favorable to the nonmovant and drawing inferences in that party's favor. We may affirm only if the judgment entered was the only one possible under the controlling law. *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 250, 106 S.Ct. 2505, 2511, 91 L.Ed.2d 202 (1986).

[4] A joint invention is the product of a collaboration between two or more persons working together to solve the problem addressed. 35 U.S.C. § 116 (1988); *Kimberly-Clark Corp. v. Procter & Gamble Distrib. Co.*, 973 F.2d 911, 917, 23 USPQ2d 1921, 1926 (Fed.Cir.1992). People may be joint inventors even though they do not physically work on the invention together or at the same time, and even though each does not make the same type or amount of contribution. 35 U.S.C. § 116. The statute does not set forth the minimum quality or quantity of contribution required for joint inventorship.

[5, 6] Conception is the touchstone of inventorship, the completion of the mental part

of invention. *Sewall v. Walters*, 21 F.3d 411, 415, 30 USPQ2d 1356, 1359 (Fed.Cir.1994). It is "the formation in the mind of the inventor, of a definite and permanent idea of the complete and operative invention, as it is hereafter to be applied in practice." *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1376, 231 USPQ 81, 87 (Fed.Cir. 1986) (citation omitted). Conception is complete only when the idea is so clearly defined in the inventor's mind that only ordinary skill would be necessary to reduce the invention to practice, without extensive research or experimentation. *Sewall*, 21 F.3d at 415, 30 USPQ2d at 1359; *see also Coleman v. Dines*, 754 F.2d 353, 359, 224 USPQ 857, 862 (Fed. Cir.1985) (conception must include every feature of claimed invention). Because it is a mental act, courts require corroborating evidence of a contemporaneous disclosure that would enable one skilled in the art to make the invention. *Coleman v. Dines*, 754 F.2d at 359, 224 USPQ at 862.

[7, 8] Thus, the test for conception is whether the inventor had an idea that was definite and permanent enough that one skilled in the art could understand the invention; the inventor must prove his conception by corroborating evidence, preferably by showing a contemporaneous disclosure. An idea is definite and permanent when the inventor has a specific, settled idea, a particular solution to the problem at hand, not just a general goal or research plan he hopes to pursue. *See Fiers v. Revel*, 984 F.2d 1164, 1169, 25 USPQ2d 1601, 1605 (Fed.Cir.1993); *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed.Cir.1991) (no conception of chemical compound based solely on its biological activity). The conception analysis necessarily turns on the inventor's ability to describe his invention with particularity. Until he can do so, he cannot prove possession of the complete mental picture of the invention. These rules ensure that patent rights attach only when an idea is so far developed that the inventor can point to a definite, particular invention.

[9, 10] But an inventor need not know that his invention will work for conception to be complete. *Applegate v. Scherer*, 332 F.2d 571, 573, 141 USPQ 796, 799 (CCPA 1964). He need only show that he had the idea; the discovery that an invention actually works is part of its reduction to practice. *Id.; see also Oka v. Youssefyeh*, 849 F.2d 581, 584 n. 1, 7 USPQ2d 1169, 1171 n. 1 (Fed.Cir.1988).

[11] Barr and Novopharm suggest that the inventor's definite and permanent idea must include a reasonable expectation that the invention will work for its intended purpose. They argue that this expectation is of paramount importance when the invention deals with uncertain or experimental disciplines, where the inventor cannot reasonably believe an idea will be operable until some result supports that conclusion. Without some experimental confirmation, they suggest, the inventor has only a hope or an expectation, and has not yet conceived the invention in sufficiently definite and permanent form. But this is not the law. An inventor's belief that his invention will work or his reasons for choosing a particular approach are irrelevant to conception. *MacMillan v. Moffett*, 432 F.2d 1237, 1239, 167 USPQ 550, 552 (CCPA 1970).

To support their reasonable expectation rule, Barr and Novopharm point to a line of cases starting with *Smith v. Bousquet*, 111 F.2d 157, 45 USPQ 347 (CCPA 1940), establishing the so-called doctrine of simultaneous conception and reduction to practice.[7] *Smith* was an interference priority contest between alleged inventors of the use of two known compounds as insecticides. Both parties asserted priority based on testing of the compounds against selected insect species. Noting the unpredictability of the experimental sciences of chemistry and biology, in particular the uncertain relationship between chemical structure and biological activity, *Smith* declined to find conception until the invention had been reduced to practice by the filing of the first patent application. *Id.* at 162, 45

7. Barr and Novopharm also point to dictum in *Biel v. Chessin*, 347 F.2d 898, 146 USPQ 293 (CCPA 1965), suggesting that conception of a method of treating the human body requires a reasonable understanding that the method will work for its intended purpose. No court has applied this dictum as controlling, and we decline to do so here.

USPQ at 352. Barr and Novopharm read this and subsequent cases to establish, or at least support, their rule that conception of an invention in an unpredictable field occurs only when the inventor has reasonable grounds to believe the invention will work.

But these cases do not stand for the proposition that an inventor can never conceive an invention in an unpredictable or experimental field until reduction to practice. In rejecting the asserted evidence of conception, *Smith* said as to one of the compounds:

> it is apparent from the record that neither [party] had in mind at the time the suggestions were originally made, nor at any time thereafter, until successful tests, if any, were made, what insects, if any, it might be effective against, or how it might be applied to produce the desired results. Accordingly, neither party had a definite idea of the "complete and operative invention" here involved prior to a successful reduction—actual or constructive—of it to practice.

Id. Thus, in awarding priority to Smith based on his constructive reduction to practice, the court relied not on the inherent unpredictability of the science, but on the absence of any evidence to corroborate an earlier conception for either of the parties.

It is undoubtedly true that "[i]n some instances, an inventor is unable to establish a conception until he has reduced the invention to practice through a successful experiment." *Amgen*, 927 F.2d at 1206, 18 USPQ2d at 1021; *Alpert v. Slatin*, 305 F.2d 891, 894, 134 USPQ 296, 299 (CCPA 1962) (no conception "where results at each step do not follow as anticipated, but are achieved empirically by what amounts to trial and error"). But in such cases, it is not merely because the field is unpredictable; the alleged conception fails because, as in *Smith*, it is incomplete. Then the event of reduction to practice in effect provides the only evidence to corroborate conception of the invention.

Under these circumstances, the reduction to practice can be the most definitive corroboration of conception, for where the idea is in constant flux, it is not definite and permanent. A conception is not complete if the subsequent course of experimentation, especially experimental failures, reveals uncertainty that so undermines the specificity of the inventor's idea that it is not yet a definite and permanent reflection of the complete invention as it will be used in practice. *See Amgen*, 927 F.2d at 1207, 18 USPQ2d at 1021 (no conception until reduction to practice where others tried and failed to clone gene using suggested strategy); *Rey-Bellet v. Engelhardt*, 493 F.2d 1380, 1387, 181 USPQ 453, 457–58 (CCPA 1974) (focusing on nature of subsequent research as indicator that inventors encountered no perplexing intricate difficulties). It is this factual uncertainty, not the general uncertainty surrounding experimental sciences, that bears on the problem of conception.

Barr and Novopharm argue for a broader reading of *Amgen* and *Fiers* in support of their reasonable expectation rule. Both of these cases involve conception of a DNA encoding a human protein—a chemical compound. Conception of a chemical substance includes knowledge of both the specific chemical structure of the compound and an operative method of making it. *Fiers*, 984 F.2d at 1169, 25 USPQ2d at 1604; *Amgen*, 927 F.2d at 1206, 18 USPQ2d at 1021; *Oka*, 849 F.2d at 583, 7 USPQ2d at 1171. The alleged inventors in *Fiers* and *Amgen* claimed conception of their respective inventions before they knew relevant chemical structure—the nucleotide sequence—so the courts found no conception until experimentation finally revealed that structure. Here, though, Burroughs Wellcome's inventions use a compound of known structure; the method of making the compound is also well known.

We emphasize that we do not hold that a person is precluded from being a joint inventor simply because his contribution to a collaborative effort is experimental. Instead, the qualitative contribution of each collaborator is the key—each inventor must contribute to the joint arrival at a definite and permanent idea of the invention as it will be used in practice.

Nor do we suggest that a bare idea is all that conception requires. The idea must be definite and permanent in the sense that it involves a specific approach to the particular

problem at hand. It must also be sufficiently precise that a skilled artisan could carry out the invention without undue experimentation. And, of course, the alleged conception must be supported by corroborating evidence. On the facts before us, it is apparent that the district court correctly ruled against Barr and Novopharm as to five of the patents, but that the court's judgment as to the sixth, the '750 patent, was premature.

The '232, '838, '130, '208, and '538 patents encompass compositions and methods of using AZT to treat AIDS. The Burroughs Wellcome inventors claim conception of these inventions prior to the NIH experiments, based on the draft British patent application. That document is not itself a conception, for conception occurs in the inventors' minds, not on paper. The draft simply corroborates the claim that they had formulated a definite and permanent idea of the inventions by the time it was prepared.

The Burroughs Wellcome inventors set out with the general goal of finding a method to treat AIDS, but by the time Broder confirmed that AZT was active against HIV, they had more than a general hope or expectation. They had thought of the particular antiviral agent with which they intended to address the problem, and had formulated the idea of the inventions to the point that they could express it clearly in the form of a draft patent application, which Barr and Novopharm concede would teach one skilled in the art to practice the inventions. The draft expressly discloses the intended use of AZT to treat AIDS. It sets out the compound's structure, which, along with at least one method of preparation, was already well known. The draft also discloses in detail both how to prepare a pharmaceutical formulation of AZT and how to use it to treat a patient infected with HIV. The listed dosages, dose forms, and routes of administration conform to those eventually approved by the FDA. The draft shows that the idea was clearly defined in the inventors' minds; all that remained was to reduce it to practice—to confirm its operability and bring it to market. *See Haskell v. Colebourne*, 671 F.2d 1362, 1365–66, 213 USPQ 192, 194 (CCPA 1982) (enabling draft patent application sufficient to corroborate conception).

An examination of the events that followed the preparation of Burroughs Wellcome's draft confirms the soundness of the conception. Broder and Mitsuya received from Burroughs Wellcome a group of compounds, known to Broder and Mitsuya only by code names, selected for testing by the Burroughs Wellcome inventors. They then tested those compounds for activity against HIV in their patented cell line. The test results revealed for the first time that one of the compounds, later revealed to be AZT, was exceptionally active against the virus.

Here, though, the testing was brief, simply confirming the operability of what the draft application disclosed. True, the science surrounding HIV and AIDS was unpredictable and highly experimental at the time the Burroughs Wellcome scientists made the inventions. But what matters for conception is whether the inventors had a definite and permanent idea of the operative inventions. In this case, no prolonged period of extensive research, experiment, and modification followed the alleged conception. By all accounts, what followed was simply the normal course of clinical trials that mark the path of any drug to the marketplace.

That is not to say, however, that the NIH scientists merely acted as a "pair of hands" for the Burroughs Wellcome inventors. Broder and Mitsuya exercised considerable skill in conducting the tests, using their patented cell line to model the responses of human cells infected with HIV. Lehrman did suggest initial concentrations to Broder, but she hardly controlled the conduct of the testing, which necessarily involved interpretation of results for which Broder and Mitsuya, and very few others, were uniquely qualified. But because the testing confirmed the operability of the inventions, it showed that the Burroughs Wellcome inventors had a definite and permanent idea of the inventions. It was part of the reduction to practice and inured to the benefit of Burroughs Wellcome.

[12] Barr and Novopharm allege error in the district court's refusal to hear their evidence of the poor predictive value of the murine retrovirus screens for activity against

HIV. Regardless of the predictive value of the murine tests, however, the record shows that soon after those tests, the inventors determined, for whatever reason, to use AZT as a treatment for AIDS, and they prepared a draft patent application that specifically set out the inventions, including an enabling disclosure. Obviously, enablement and conception are distinct issues, and one need not necessarily meet the enablement standard of 35 U.S.C. § 112 to prove conception. *See Fiers*, 984 F.2d at 1169, 25 USPQ2d at 1605. But the enabling disclosure does suffice in this case to confirm that the inventors had concluded the mental part of the inventive process—that they had arrived at the final, definite idea of their inventions, leaving only the task of reduction to practice to bring the inventions to fruition.

The question is not whether Burroughs Wellcome reasonably believed that the inventions would work for their intended purpose, the focus of the evidence offered by Barr and Novopharm, but whether the inventors had formed the idea of their use for that purpose in sufficiently final form that only the exercise of ordinary skill remained to reduce it to practice. *See MacMillan v. Moffett*, 432 F.2d at 1239, 167 USPQ at 552 (Inventor's "reasons or lack of reasons for including U–5008 are not relevant to the question of conception. The important thing is that he did think in definite terms of the method claimed."). Whether or not Burroughs Wellcome believed the inventions would in fact work based on the mouse screens is irrelevant.

We do not know precisely when the inventors conceived their inventions, but the record shows that they had done so by the time they prepared the draft patent application that thoroughly and particularly set out the inventions as they would later be used. The district court correctly ruled that on this record, the NIH scientists were not joint inventors of these inventions.

[13] The '750 patent is another question. It claims "[a] method of increasing the number of T-lymphocytes in a human infected with the [HIV] virus comprising administering to said human an effective amount of" AZT. Novopharm argues that there is no evidence, under any test of inventorship, that the Burroughs Wellcome inventors conceived of this invention until after the Phase I patient study conducted by Broder and Yarchoan revealed that AZT could lead to increased levels of T-cells in AIDS patients.

Novopharm is right that the record is devoid of any statement that the inventors thought AZT could raise a patient's T-cell levels, but evidence need not always expressly show possession of the invention to corroborate conception. The district court held that the record supported conception as a matter of law, concluding that "an increase in T-lymphocyte count was an 'obvious,' natural phenomenon known to the [Burroughs Wellcome] inventors that would result from the inhibition of a retrovirus." *Burroughs Wellcome Co. v. Barr Lab., Inc.*, 828 F.Supp. at 1213. Burroughs Wellcome argues that this conclusion was proper because increased T-cell count is simply an obvious property or use of the greater discovery at issue here, the treatment of HIV infection with AZT. Because an increase in T-lymphocytes follows inevitably from treatment of AIDS patients with AZT, Burroughs Wellcome says, Broder and Yarchoan merely observed that the method invented by the Burroughs Wellcome inventors had qualities that the inventors failed to perceive. Burroughs Wellcome says this is not an inventive contribution to the claims of any of the AZT patents.

[14] But even though all six patents arise from the same parent application and are subject to terminal disclaimers to avoid rejection for obviousness-type double patenting, each patent claims a different invention.[8] *See In re Longi*, 759 F.2d 887, 892, 225

8. We must assume for the purposes of this case that the '750 patent is drawn to an invention different from each of the other five patents. The parties do not ask us to decide whether claims drawn to an effect or mechanism of action of AZT—its ability to raise T-cell count—reach the same invention as (that is, are inherent in) claims drawn to use of the drug to treat HIV infection or AIDS, and we express no opinion on that. The dissent therefore goes beyond the issues presented and the record before us to decide on the basis of what the dissenting judge thinks he knows. That is not the role of an appellate court.

USPQ 645, 648 (Fed.Cir.1985) (inventor can get only one patent for any single invention). It is true that the Patent Office determined that the method of the '750 patent would have been obvious to those skilled in the art in light of the inventions claimed in the other patents. That is, however, irrelevant to the question whether the Burroughs Wellcome inventors had conceived of the invention before they learned the results of the Phase I trials. For conception, we look not to whether one skilled in the art could have thought of the invention, but whether the alleged inventors actually had in their minds the required definite and permanent idea. *Cf. Bosies v. Benedict*, 27 F.3d 539, 543, 30 USPQ2d 1862, 1865 (Fed.Cir.1994) (testimony of noninventor as to noninventor's understanding of inventor's written formula insufficient to prove conception). The record does not now support resolution of this question as a matter of law.

The alleged conception is supported by testimony of Burroughs Wellcome's experts, Burroughs Wellcome's draft Phase I protocol, and the same draft patent application that corroborates conception of the other five inventions. The experts testified that those skilled in the art at the time expected increased immune function to accompany inhibition of HIV. The draft patent application discloses that HIV preferentially destroys T-cells, that AIDS is associated with progressive depletion of T-cells, and that AZT is an effective treatment for HIV infection. Finally, the draft protocol directs the administrators of the Phase I study to monitor patients' T-lymphocyte count. This evidence supports an inference that the Burroughs Wellcome inventors did have the necessary definite and permanent idea, for, given the virus' effect on T-lymphocytes, it seems logical to conclude that stopping the virus might reverse the process of T-cell destruction and restore the body's immune system to a pre-infection state. If this were the only evidence in the record, the court's judgment would be sustained.

But Novopharm offered evidence suggesting that one skilled in the art would not have expected T-cell count to rise. On deposition, Broder testified that prior to the first patient study, "no one knew whether there was such a thing as recovery" of T-cells, based on the NIH's experience with suramin, a drug that entered clinical trials before AZT. Although suramin showed some activity against HIV, inhibition of the retrovirus apparently was not accompanied by increases in T-cell count or restoration of immune functions. Of course, there might be any number of other explanations for the results of the suramin trials; but they might suggest that although those skilled in the art recognized the significance of T-lymphocyte levels in HIV infection and AIDS, they might have expected inhibition of the virus simply to halt the continuing destruction of T-cells, not to increase T-cell count and restore immune function. This could support an inference that the inventors themselves did not conceive the invention prior to the Phase I study.

Novopharm also contends that Burroughs Wellcome prepared its Phase I protocol in collaboration with Broder and the NIH, possibly from a draft protocol prepared by Broder and Yarchoan pursuant to their study of suramin. These contentions are relevant to the conception inquiry for they tend to undermine the corroborative value of the draft protocol, and might even support joint inventorship based on that draft. *See Coleman v. Dines*, 754 F.2d at 360, 224 USPQ at 863 (document's co-author cannot be considered sole inventor of invention disclosed in document without further proof). Because under Rule 50(a) all inferences must be taken against the moving party, the court's ruling on the '750 patent was inappropriate, and we vacate the judgment to that extent and remand for further proceedings.

Conclusion

Accordingly, the judgment of the United States District Court for the Eastern District of North Carolina is affirmed in part, vacated in part, and remanded.

COSTS

All parties will bear their own costs.

AFFIRMED IN PART, VACATED IN PART, AND REMANDED.

LOURIE, Circuit Judge, concurring-in-part and dissenting-in-part.

I concur in the majority's decision with respect to the '232, '838, '130, '208, and '538 patents, and join the opinion except for the following:

I do not agree that reduction to practice is corroboration of conception and that the completeness of a conception is affected by subsequent experimental success or failure. These statements confuse the idea of conception with both corroboration and reduction to practice. A conception must be judged as to its completeness in relation to the invention being claimed. It must also be corroborated by evidence independent of the inventor. If subsequent experimentation shows that an invention that was only conceived does not work, that fact does not vitiate the earlier conception. A conception not later reduced to practice may have little significance, but it is important that we not confuse concepts. The conception was still a conception. It is of course possible for an invention to be reduced to practice constructively, *i.e.*, by filing a patent application, rather than actually, by doing the work, in which case the reduction to practice clearly says nothing about the completeness of the conception. Moreover, what matters, in addition to the completeness of a conception, is its date. Corroboration must be of the date of the conception. If the only "corroboration" of the conception is its reduction to practice, corroboration has not occurred concerning the alleged date of conception. Finally on this point, reduction to practice by the inventor is not corroboration because corroboration must be independent of the inventor. Corroboration is not a demonstration that the conceived invention works; it is evidentiary proof that the mental act of invention occurred on a certain date.

I also believe that the issue of joint inventorship is irrelevant here and therefore confusing. If the Burroughs Wellcome inventors had a complete conception, as we hold, then the NIH scientists were not inventors because the invention had already been made, not because of any shortcomings in their inventive contributions. Thus, there is no need to discuss joint inventorship at all.

I respectfully dissent from the vacating of the court's judgment concerning the '750 patent. I believe that the method of the '750 patent is an inherent, inevitable result of the practice of the other method patents claiming treatment of HIV or AIDS. It seems to be the (or a) mechanism by which the other methods find their use.

Even if it is true that the first verification or articulation of the increase in the T-cell count occurred in the hands of NIH scientists, this finding inures to the benefit of those who conceived the method of treatment that led to it. The method of the '750 patent is merely a refined definition of the method of the '232 patent, which issued from the original application. The '130 and '208 patents, which also came from applications later filed with the '750 and the composition patents, are also modifications of the original filing. It is common practice for applicants to claim all aspects of their invention and that is what appears to have happened here. An inventor is entitled to the inherent benefits that flow from his or her invention. It is improper to split the inventorship of what is one invention merely because the means by which it was achieved was later verified by scientists acting pursuant to the original conceivers.

The PTO of course issued these patents. During its examination, it determined that the '750 method was obvious over the '232 method. Given a terminal disclaimer, this led to the grant of the patent. More than being obvious, however, the method was inherent in the '232 method and therefore lacking in novelty. *See* 35 U.S.C. § 102 (1988). If, as I believe, the '750 invention does lack novelty over the other patents, its validity may be in question on the ground of double patenting because a terminal disclaimer is not effective to cure a double patenting problem when the inventions are the same. As long as the inventive entities are also the same, however, it doesn't really matter.

Even assuming that the '750 method is a separate invention, the majority concedes that evidence supports an inference that the Burroughs Wellcome inventors alone conceived the method. The majority goes off

the track, however, in relying on Novopharm's offer of evidence that one would not have expected the T-cell count to rise. This is irrelevant if Burroughs Wellcome's inventors had the conception, because the opinion earlier correctly holds that a reasonable expectation of success is not necessary to a conception.

The majority here is inviting the trial court on remand and motion, *see* 35 U.S.C. § 256 (1988), to partially split the inventorship, and presumably also the ownership, of this related collection of patents claiming the physical act of "treating" and the result which the treatment accomplishes. This makes no sense. It amounts to deciding that treating a person in pain with aspirin is one invention and invoking the pain-relieving mechanism by means of that treatment is another. One cannot apparently treat HIV-infected humans with AZT without also increasing the level of T-lymphocytes. The panel is thus inconsistent in upholding the conclusion of the trial court that Burroughs Wellcome's scientists alone conceived the invention of using AZT to treat HIV infection, but then failing to arrive at the same conclusion regarding a patent claiming one of the sequelae of that use.

The real result of the majority's vacating the court's decision on the '750 patent is that, while it may believe that it is affirming the decision on the other patents, it may in practical effect be destroying Burroughs Wellcome's exclusivity for its invention and creating a whole new set of questions. If the trial court joins the NIH inventors, and NIH has licensed the patent to companies intending to sell AZT, will those companies infringe the '232 and other patents? Is the terminal disclaimer still valid, lacking the consent of one of the assignees? Without a valid terminal disclaimer, is the '750 patent valid? While these questions are not before us, exploring them illustrates the strange consequences of the majority's decision. On the other hand, if the trial court confirms its finding that the T-lymphocyte "invention" was essentially the same invention and inured to the benefit of Burroughs Wellcome, the remand will have been superfluous. Useless and inefficient litigation and burdening of the courts will have resulted.

The trial court's decision should be affirmed across the board because it correctly found that the Burroughs Wellcome inventors solely conceived and are entitled to the inventive benefit of all the claimed inventions.

decision based on the record made at the hearing. *Id.*

The Customs Service's regulations track the statutory requirements for both stages of the revocation process, although the regulations characterize the first stage of the proceedings as "preliminary" and the second stage as "formal." *See* 19 C.F.R. § 111.59 (1993). What the regulations refer to as the "notice of preliminary proceedings" contains a copy of the proposed statement of charges, an invitation to show cause why formal proceedings should not be instituted, an advisement that formal proceedings are available, and a direction that a response to the notice must be filed within 30 days. *See id.* Those papers fully comport with the requirements of the first two sentences of the revocation statute, section 1641(d)(2)(B).

The regulations next provide for the Customs Service to decide, at the conclusion of the preliminary proceedings, whether revocation is still warranted. *See* 19 C.F.R. § 111.61 (1993). That provision in the regulations comports with the first portion of the third sentence of section 1641(d)(2)(B).

Finally, the regulations provide that in the event the Customs Service decides to go forward with revocation proceedings, it must hold a formal hearing, preceded by service of a notice of the hearing and a statement of the charges. *See* 19 C.F.R. §§ 111.62–111.64 (1993). Those provisions of the regulations accord with the requirements of the second portion of the third sentence of section 1641(d)(2)(B).

In sum, although the regulations characterize the revocation process as divided into "preliminary" and "formal" stages, those two stages are simply component parts of the unitary revocation proceeding described in section 1641(d)(2)(B). The commencement of the "preliminary" stage, as defined in the regulations, marks the beginning of the statutory revocation proceeding.

The statute of limitations is satisfied if the statutory revocation proceeding is "instituted by the appropriate service of written notice" within five years of the alleged violation. 19 U.S.C. § 1641(d)(4) (1988). The written notice must include a "notice .... to show cause why a license or permit issued under this section should not be revoked or suspended." *Id.* § 1641(d)(2)(B). The materials served on Mr. Urbano at the "preliminary proceedings" stage included such a notice. The statute of limitations was therefore satisfied in March 1993 when the "Notice of Preliminary Proceedings" and "Proposed Notice to Show Cause and Statement of Charges" were served on Mr. Urbano.

Mr. Urbano argues that the statute of limitations should not be construed in this fashion, because it would allow the government to satisfy the limitations period by initiating preliminary proceedings, but then to delay the initiation of formal proceedings indefinitely, thus effectively depriving the customs broker of the protection of the statute of limitations. While it is true that there is no restriction governing the time within which the government must proceed from the first stage of the revocation proceedings to the second, that is simply a consequence of the way in which the revocation statute is written. It would be inappropriate for us to recast the limitations statute to be triggered by the service of written notice of the formal hearing specified in section 1641(d)(2)(B), simply because it might be preferable to require the government to proceed to a formal revocation hearing within a fixed time period after the alleged violations.

AFFIRMED.

Gilbert P. HYATT, Appellant,

v.

Gary W. BOONE, Cross-Appellant.

Nos. 96-1514, 96-1515.

United States Court of Appeals,
Federal Circuit.

June 17, 1998.

Rehearing Denied; Suggestion for Rehearing In Banc Declined
Aug. 26, 1998.

In patent interference proceeding No. 102,598, relating to computer formed on a

single integrated circuit chip, the Board of Patent Appeals and Interferences entered judgment against patentee and cancelled relevant patent claims, but also entered judgment against applicant. Patentee appealed, and applicant cross-appealed. The Court of Appeals, Pauline Newman, Circuit Judge, held that: (1) patentee's earlier-filed application did not sufficiently describe invention that was subject of interference count for purpose of establishing priority; (2) applicant's alleged technical violations of rule governing continuation applications did not warrant reversal of finding that chain of priority was not broken; (3) Board was not required to rule on patentability of applicant's claims once applicant requested conversion to statutory invention registration (SIR); and (4) Board was required to determine priority and recognize applicant's status as prior inventor.

Affirmed, modified in part.

1. Patents ⇐90(1)

First person to conceive invention is generally first inventor, for priority purposes, provided that when first to conceive invention is last to reduce it to practice, person who was first to conceive must have exercised reasonable diligence to his own actual or constructive reduction to practice, from a time prior to conception by the other. 35 U.S.C.A. § 102(g).

2. Patents ⇐106(3)

During an interference proceeding evidence may be presented of conception, reduction to practice, and diligence, as appropriate to the positions of the parties, or a party may rely on the patent document to establish the facts of priority of invention.

3. Patents ⇐98

The filing of a patent application serves as conception and constructive reduction to practice of the subject matter described in the application.

4. Patents ⇐98

In filing of patent application, there is no need for proof or corroboration of subject matter that is included in application unless date earlier than filing date is sought to be established; thus, inventor need not provide evidence of either conception or actual reduction to practice when relying on content of patent application.

5. Patents ⇐106(1)

When a party to an interference seeks the benefit of an earlier-filed United States patent application, the earlier application must contain a written description of the subject matter of the interference count, and must meet the requirement that the written description enables any person skilled in the art to make and use the same. 35 U.S.C.A. §§ 112, 120.

6. Patents ⇐113(6)

Court of Appeals reviews for clear error findings of Board of Patent Appeals and Interferences as to patent application's compliance with written description requirement, which is question of fact.

7. Patents ⇐101(4)

Patent claims as filed are part of the specification, and may provide or contribute to compliance with written description requirement. 35 U.S.C.A. § 112.

8. Patents ⇐106(1)

For an earlier-filed patent application to serve as constructive reduction to practice of the subject matter of an interference count, the applicant must describe the subject matter of the count in terms that establish that he was in possession of the later-claimed invention, including all of the elements and limitations presented in the count, at the time of the earlier filing.

9. Patents ⇐99

Although known details need not be included in a patent specification, it must be shown, when an explicit limitation in an interference count is not present in the written description whose benefit is sought, that a person of ordinary skill would have understood, at the time the patent application was filed, that the description requires that limitation.

10. Patents ⇐99

It is insufficient as written description, for purposes of establishing priority of invention, to provide a specification that does not

unambiguously describe all limitations of the count.

11. Patents ⇐106(1)

Board of Patent Appeals and Interferences did not clearly err in finding that patentee's earlier-filed patent application did not adequately describe invention that was subject of interference count, for priority purposes, as subject matter missing from earlier application was not known details, but significant claim limitations, and missing subject matter was not shown to be part of the prior art that would be understood as part of the description of the subject matter of the count. 35 U.S.C.A. § 112.

12. Patents ⇐106(1)

Requirement that specification of earlier-filed patent application "necessarily" describe entire subject matter of interference count, in order to claim priority based on earlier application, was equivalent to standard that applicant convey with reasonable clarity to those skilled in the art that, as of filing date sought, applicant was in possession of invention. 35 U.S.C.A. § 112.

13. Patents ⇐99

Written description of earlier-filed application must include all of the limitations of the interference count, to establish priority based on earlier application, or applicant must show that any absent text is necessarily comprehended in the description provided and would have been so understood at the time the patent application was filed. 35 U.S.C.A. § 112.

14. Patents ⇐98, 110

Alleged technical violations of rule governing continuation applications for patent did not warrant reversal of finding that chain of priority between application involved in interference count and original application was not broken, in view of Patent and Trademark Office's acceptance of allegedly deficient applications as in compliance with rule. 37 C.F.R. § 1.60 (1996).

15. Administrative Law and Procedure ⇐500

Regularity of routine administrative procedures is presumed, and departure therefrom, should such have occurred, is not grounds of collateral attack.

16. Patents ⇐115

Inventor of statutory invention registration (SIR) has same rights that a patent provides to prevent others from patenting the invention, and inventor preserves ability to protect the right to practice his own prior invention as against any later inventor, while foregoing the right to exclude others even if he is the prior inventor. 35 U.S.C.A. § 157.

17. Patents ⇐106(1)

Board of Patent Appeals and Interferences was not required to rule on patentability of applicant's claims, in interference proceeding, once applicant requested conversion to statutory invention registration (SIR), although Board was required to determine whether applicant or patentee had prevailed on issue of priority. 35 U.S.C.A. § 157.

18. Patents ⇐106(1)

In patent interference proceeding, priority issues that have been fully developed and presented for decision should be decided. 35 U.S.C.A. § 135(a).

19. Patents ⇐106(1)

Applicant's waiver of right to patent, in accordance with statutory invention registration (SIR), did not preclude Board of Patent Appeals and Interferences from recognizing applicant's status as prior inventor in interference proceeding. 35 U.S.C.A. § 157.

John M. DiMatteo, Patterson, Belknap, Webb & Tyler LLP, of New York City, argued for appellant. With him on brief was Gregory L. Roth, Law Offices of Gregory L. Roth, of La Palma, California.

Louis Touton, Jones, Day, Reavis & Pogue, of Los Angeles, California, argued for cross–appellant. Of counsel on brief was Jay M. Cantor, Spencer, Frank & Schneider, of Washington, DC.

Before NEWMAN, MICHEL, and PLAGER, Circuit Judges.

PAULINE NEWMAN, Circuit Judge.

The parties to Patent Interference No. 102,598 are Gilbert P. Hyatt, inventor of United States Patent No. 4,942,516 entitled

"Single Chip Integrated Circuit Computer Architecture" (the '516 patent), and Gary W. Boone, inventor of patent application Serial No. 07/473,541 entitled "Variable Function Programmed Systems" (the '541 application). Mr. Hyatt appeals the decision of the Board of Patent Appeals and Interferences, entering judgment against him and cancelling the relevant claims of his '516 patent. Mr. Boone cross-appeals the Board's entry of judgment against him. We affirm the Board's decision,[1] with modification of the judgment to declare Boone the prevailing party in the interference.

DISCUSSION

Determination of priority of invention invokes a complex body of procedural and substantive law, applied in the first instance in administrative proceedings in accordance with 35 U.S.C. § 135(a) ("The Board of Patent Appeals and Interferences shall determine questions of priority of the inventions and may determine questions of patentability.") The interference proceeding implements the principle of United States law that the right to a patent derives from priority of invention, not priority of patent application filing.

[1, 2] The general rule is that the first person to conceive the invention is the first inventor, *see* Irving Kayton, *The United States Patent as a Legal Instrument, in 1 Patent Practice* 2–1, 2–39 (Irving Kayton and Karyl S. Kayton eds., 4th ed. 1989) ("The earliest possible date of invention, therefore, is the date of conception."), provided that when the first to conceive the invention is the last to reduce it to practice, the person who was first to conceive must have exercised reasonable diligence to his own actual or constructive reduction to practice, "from a time prior to conception by the other." 35 U.S.C. § 102(g). *See* Charles L. Gholz, *Interference Practice, in* 6 *Patent Practice, supra*, 24–1, 24–6(c); *Paulik v. Rizkalla*, 760 F.2d 1270, 1272, 226 USPQ 224, 225 (Fed.Cir. 1985) (in banc). Thus, during an interference proceeding evidence may be presented of conception, reduction to practice, and diligence, as appropriate to the positions of the parties, *see id.; see generally* Gholz, *supra*, at 24–1, or a party may rely on the patent document to establish the facts of priority of invention. *See* Gholz, *supra*, at 24–45.

The contested invention is a computer formed on a single integrated circuit chip, having specified circuits and functions. The sole count of the interference is:

A computer on a chip comprising:

an integrated circuit chip having a computer implemented thereon;

an integrated circuit main memory storing computer instructions, wherein said integrated circuit main memory is included on said integrated circuit chip;

an integrated circuit operand memory storing operands, wherein said integrated circuit operand memory is included on said integrated circuit chip; and

an integrated circuit processing circuit processing the operands stored by said integrated circuit operand memory in response to the instructions stored in said integrated circuit main memory, wherein said processing circuit is included on said integrated circuit chip.

The interference contest was initiated by Boone after Hyatt's '516 patent issued. Boone followed the procedure of copying certain of Hyatt's patent claims into his pending application and asking the patent examiner to "declare" the interference. 37 C.F.R. § 1.607 (1990). The examiner so acted. *See* 37 C.F.R. § 1.611 (1990).

Both parties claimed the benefit of earlier-filed patent applications, relying on the earlier applications for constructive reduction to practice of the subject matter of the count. *See* 37 C.F.R § 1.626 (1990). Conception is not at issue in this appeal, and neither party presented evidence of actual reduction to practice. At the Motions stage from which the Board's decision evolved, the only issue was each party's entitlement to certain asserted dates of constructive reduction to practice.

Boone was granted an effective filing date, through a chain of nine prior applications, of

1. *Hyatt v. Boone*, Patent Interference No. 102,598 (Bd. Pat.App. & Inter. Sept. 19, 1995) (Decision after Final Hearing); *Hyatt v. Boone*, Patent Interference No. 102,598 (Bd. Pat.App. & Inter. May 10, 1996) (Decision on Reconsideration).

an application filed on July 19, 1971. Hyatt was granted an effective filing date, through a chain of four prior applications, of an application filed on December 14, 1977. The Board denied Hyatt the benefit of the filing date of his December 28, 1970 application No. 05/101,881 (the '881 application) as to the subject matter of the count. Hyatt disputes the denial of the '881 application filing date, and also challenges the date awarded to Boone.

I

HYATT'S '881 APPLICATION

[3, 4] The filing of a patent application serves as conception and constructive reduction to practice of the subject matter described in the application. *Yasuko Kawai v. Metlesics*, 480 F.2d 880, 885, 178 USPQ 158, 162 (CCPA 1973) ("[T]he act of filing the United States application has the legal effect of being, constructively at least, a simultaneous conception and reduction to practice of the invention."); *see Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1376, 231 USPQ 81, 87 (Fed.Cir.1986) ("constructive reduction to practice occurs when a patent application on the claimed invention is filed"); *In re Glass*, 492 F.2d 1228, 1232, 181 USPQ 31, 34 (CCPA 1974). There is no need for proof or corroboration of the subject matter that is included in the application unless a date earlier than the filing date is sought to be established. *Yasuko Kawai*, 480 F.2d at 886, 178 USPQ at 163 ("the written specification in the application is the evidence proving the invention of that which is reduced to practice"). Thus the inventor need not provide evidence of either conception or actual reduction to practice when relying on the content of the patent application.

[5] However, the patent application must comply with the legal requirements for support of the interference count. When a party to an interference seeks the benefit of an earlier-filed United States patent application, the earlier application must meet the requirements of 35 U.S.C. § 120[2] and 35 U.S.C. § 112 ¶ 1[3] for the subject matter of the count. The earlier application must contain a written description of the subject matter of the interference count, and must meet the enablement requirement. *Fiers v. Revel*, 984 F.2d 1164, 1170, 25 USPQ2d 1601, 1606 (Fed.Cir.1993) (section 112 paragraph 1 must be met by the earlier application). The Board found that Hyatt's '881 application did not provide the requisite written description; the Board did not decide the question of enablement.

A

[6] We review the Board's findings on the standard of clear error, for compliance with the written description requirement is a question of fact. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563, 19 USPQ2d 1111, 1116 (Fed.Cir.1991). Hyatt relies as written description on the text of claim 40 as that claim was originally filed in the '881 application, viewed with the entire specification.

[7] The claims as filed are part of the specification, and may provide or contribute to compliance with § 112. *See Northern Telecom, Inc. v. Datapoint Corp.*, 908 F.2d 931, 938, 15 USPQ2d 1321, 1326 (Fed.Cir. 1990) (the original claims are part of the patent specification); *In re Benno*, 768 F.2d 1340, 1346, 226 USPQ 683, 686–87 (Fed.Cir. 1985); *In re Frey*, 35 C.C.P.A. 970, 166 F.2d 572, 575, 77 USPQ 116, 119 (CCPA 1948). Hyatt's original claim 40 is for a data processing system implemented on a single integrated circuit chip, as follows:

> 40. An electronic data processing system including read only memory means, alterable memory means and program means, said system being implemented on a single integrated circuit chip.

2. **35 U.S.C. § 120. Benefit of earlier filing date in the United States.**

> An application for patent for an invention disclosed in the manner provided by the first paragraph of section 112 of this title in an application previously filed in the United States ... shall have the same effect, as to such invention, as though filed on the date of the prior application....

3. **35 U.S.C. § 112 ¶ 1.**

> [The application must contain] a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same....

There is no other mention in the '881 specification of a single integrated circuit chip, although other electronic data systems are extensively described.

Hyatt's position is that the text of claim 40 describes the subject matter of the interference count, in that the "read only memory means" of claim 40 is the same as the "integrated circuit main memory storing computer instructions" of the count, the "alterable memory means" of claim 40 is the same as the "integrated circuit operand memory storing operands" of the count, and the "program means" of claim 40 is the same as the "integrated circuit processing circuit" of the count. Hyatt states that the '881 specification contains detailed descriptions of various computer circuits, which supplement the text of claim 40 in that the specification describes a computer made up of numerous integrated circuits mounted on multiple printed circuit boards and comprising a "physically distributed, operatively dispersed system."

The Board held that the written description must be sufficient, when the entire specification is considered, that the "necessary and only reasonable construction" that would be given it by a person skilled in the art is one that clearly supports each positive limitation in the count. The Board found that the term "program means" in claim 40 is used to describe only computer instructions or as a modifier of "program control means," and does not describe or require the interpretation that the program processes the operands stored by the alterable memory in accordance with instructions stored in the read only memory, as is required by the count. The Board also found that the "read only memory means" of claim 40 need not be a main memory storing computer instructions, and that the "alterable memory means" of claim 40 need not be an operand memory storing operands. Thus the Board found that original claim 40 could be read as describing subject matter other than that of the count, and thus did not establish that Hyatt was in possession of the invention of the count. The Board found that the parts of the written description that are lacking from claim 40 are not provided elsewhere in the '881 specification, whose systems and circuitry neither describe nor suggest a computer on a single chip. The Board concluded that "[w]hile two memories and a computer program may generally constitute a data processing system of some sort, they do not describe the invention set forth by the count."

Rejecting Hyatt's argument, supported by testimony of witnesses, that the absent description would have been apparent to persons of skill in this field, the Board stated that "if 'program means' can be a circuit (processor) that responds to a program as indicated by [Hyatt's] witnesses, it is at least as likely that it can be a memory that merely stores a program without processing operands." The Board held that witnesses can not "establish facts which the disclosure itself should provide," citing *In re Smyth*, 38 C.C.P.A. 1130, 189 F.2d 982, 990, 90 USPQ 106, 112 (CCPA 1951). Hyatt challenges these findings and conclusions, as well as the Board's legal standard for determining compliance with the written description requirement.

B

[8–10] For an earlier-filed application to serve as constructive reduction to practice of the subject matter of an interference count, the applicant must describe the subject matter of the count in terms that establish that he was in possession of the later-claimed invention, including all of the elements and limitations presented in the count, at the time of the earlier filing. Although Hyatt is correct that known details need not be included in a patent specification, *see In re Eltgroth*, 57 C.C.P.A. 833, 419 F.2d 918, 921, 164 USPQ 221, 223 (CCPA 1970) ("This court has often observed that minutiae of descriptions or procedures perfectly obvious to one of ordinary skill in the art yet unfamiliar to laymen need not be set forth."), when an explicit limitation in an interference count is not present in the written description whose benefit is sought it must be shown that a person of ordinary skill would have understood, at the time the patent application was filed, that the description requires that limitation. As discussed in *Martin v. Mayer*, 823 F.2d 500, 505, 3 USPQ2d 1333, 1337 (Fed.Cir.1987), "It is 'not a question of whether one skilled in the art *might* be able

to construct the patentee's device from the teachings of the disclosure.... Rather, it is a question whether the application necessarily discloses that particular device.'" (quoting *Jepson v. Coleman*, 50 C.C.P.A. 1051, 314 F.2d 533, 536, 136 USPQ 647, 649–50 (CCPA 1963)). *See Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1571–72, 41 USPQ2d 1961, 1966 (Fed.Cir.1997). It is insufficient as written description, for purposes of establishing priority of invention, to provide a specification that does not unambiguously describe all limitations of the count. *See, e.g., Wagoner v. Barger*, 463 F.2d 1377, 1380, 175 USPQ 85, 86–87 (CCPA 1972); *Dyer v. Field*, 55 C.C.P.A. 771, 386 F.2d 466, 156 USPQ 85 (CCPA 1967); *Bocciarelli v. Huffman*, 43 C.C.P.A. 873, 232 F.2d 647, 109 USPQ 385 (CCPA 1956).

[11] Hyatt and Boone presented conflicting views of the knowledge of a person of ordinary skill in the field of the invention at the time the '881 patent application was filed, and disputed whether such a person would have understood the text of Hyatt's original claim 40 as describing all of the limitations of the count. Hyatt's witnesses testified that a person of skill in this field would have known that the program means processes the operands in accordance with the read-only memory instructions, and would have readily understood that the program means, read only memory means, and alterable memory means cooperate in the way stated in the count. The Board criticized this testimony on the ground that although Hyatt's witnesses stated that it was well known that a data processing system must include a processing circuit of some sort, they did not address "whether a data processing system must necessarily include the specific processing circuit required by the count." We have not been shown clear error in the Board's findings as to the content of the written description, and the conclusion that the missing subject matter was not known details, but significant claim limitations; the missing subject matter was not shown to be part of the prior art that would be understood as part of the description of the subject matter of the count.

[12] Hyatt states that even if the Board's findings are not clearly erroneous as to the content of the written description, the Board applied an incorrect legal standard in requiring that the specification "necessarily" describe the entire subject matter of the count. Hyatt states that a separate body of precedent, typified by *Vas–Cath Inc. v. Mahurkar*, 935 F.2d 1555, 19 USPQ2d 1111 (Fed.Cir. 1991), states a different and better standard. In *Vas–Cath* the court stated that the applicant must "convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention." *Id.* at 1563–64, 935 F.2d 1555, 19 USPQ2d at 1117. Other cases have used the same words in assessing the adequacy of the written description. *See, e.g., Fujikawa v. Wattanasin*, 93 F.3d 1559, 1570, 39 USPQ2d 1895, 1904 (Fed.Cir.1996) ("the disclosure need only reasonably convey to persons skilled in the art that the inventor had possession of the subject matter in question"); *Fiers v. Revel*, 984 F.2d at 1170, 25 USPQ2d at 1606 (same); *In re Kaslow*, 707 F.2d 1366, 1375, 217 USPQ 1089, 1096 (Fed. Cir.1983) (same). Hyatt states that he readily met this requirement, in that original claim 40 of his '881 application reasonably conveyed to persons of skill in this field that he possessed the invention of the count.

[13] Hyatt argues that "reasonably conveys to the artisan" is a less rigorous and more reasonable measure of the written description requirement than the "necessary and only reasonable construction" standard that the Board applied. Precedent has used both phrases, as well as others. *See, e.g., In re Wertheim*, 646 F.2d 527, 538–39, 209 USPQ 554, 565 (CCPA 1981) (the disclosure relied on must "constitute[ ] a full, clear, concise and exact description ... of the invention claimed"). We do not view these various expressions as setting divergent standards for compliance with § 112. In all cases, the purpose of the description requirement is "to ensure that the inventor had possession, as of the filing date of the application relied on, of the specific subject matter later claimed by him." *In re Edwards*, 568 F.2d 1349, 1351–52, 196 USPQ 465, 467 (CCPA 1978). Thus, the written description must include all of the limitations of the interference count, or the applicant must show that any absent text is necessarily comprehended in the description provided and

would have been so understood at the time the patent application was filed.

The Board did not clearly err in finding that Hyatt did not establish in the '881 application's written description that he possessed the entire subject matter of the count. This finding comports with the criterion not only of whether the description conveyed to the artisan the specific subject matter of the count, but also of whether the applicant established that this was the necessary construction of that description. The written description must include the limitations of the count with sufficient clarity and specificity that "persons of ordinary skill in the art will recognize from the disclosure that appellants invented processes including those limitations," *In re Wertheim*, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976). The denial to Hyatt of benefit of the '881 application date as constructive reduction to practice of the interference count is affirmed.

II

BOONE'S '565 APPLICATION

[14] Hyatt objected to the action of the administrative patent judge in according Boone the benefit of the July 19, 1971 filing date of application Serial No. 163,565 (the '565 application), the first of ten applications culminating in the '541 application in interference. Hyatt's objection is that at least two of these ten applications are invalid continuation applications, thus breaking the chain of priority. Hyatt states that Boone's second and eighth applications, both of which were filed under the "streamlined" procedures of 37 C.F.R. § 1.60 (Rule 60) with photocopies of the prior specification and oath, contained amended claims and thus could not have been filed under Rule 60, but required a new oath. Boone concedes the facts of these filings, but argues that these are not flaws, or not flaws fatal to his entitlement to trace priority through the chain.

[15] Rule 60, at the time of Boone's first challenged continuation application in 1973, was as follows:

> **37 C.F.R. § 1.60 [1973].** A continuation or divisional application ... which discloses and claims only subject matter disclosed in a prior application may be filed as a separate application before the patenting or abandonment of or termination of proceedings on the prior application. If the application papers comprise a copy of the prior application as filed, signing and execution by the applicant may be omitted.... Only amendments reducing the number of claims or adding a reference to the prior application (§ 1.78(a)) will be entered before calculating the filing fee and granting of the filing date.

By 1987, when Boone's eighth continuation was filed, Rule 60 had been elaborated as follows:

> **37 C.F.R. § 1.60(b) [1987].** An applicant may omit signing of the oath or declaration in a continuation or divisional application if ... (2) applicant files a true copy of the prior complete application as filed including the specification (including claims), drawings, oath or declaration showing the signature or an indication it was signed, and any amendments referred to in the oath or declaration filed to complete the prior application.... Only amendments reducing the number of claims or adding a reference to the prior application (§ 1.78(a)) will be entered before calculating the filing fee and granting of the filing date.

From the text of these provisions, it is not clear whether any technical violation of Rule 60 actually occurred with the presentation of amended claims. The administrative patent judge found none. No objection to compliance with Rule 60 was raised by the PTO at the time these applications were filed and prosecuted. The issue here raised is not one of substantive continuity of disclosure, but solely of whether a photocopy of the prior oath, instead of a new oath, was acceptable for filing, when it was in fact accepted for filing. Any technical deficiency in meeting the formal requirements of Rule 60 must be viewed in light of the agency's acceptance of the applications as in compliance with the Rule. Regularity of routine administrative procedures is presumed, and departure therefrom, should such have occurred, is not grounds of collateral attack. Courts should not readily intervene in the day-to-day operations of an administrative agency, especially when the agency practice is in straightfor-

ward implementation of the statute. *Cf. Vermont Yankee Nuclear Power Corp. v. Natural Resources Defense Council, Inc.*, 435 U.S. 519, 98 S.Ct. 1197, 55 L.Ed.2d 460 (1978) ("[T]his Court has for more than four decades emphasized that the formulation of procedures was basically to be left within the discretion of the agencies to which Congress had confided the responsibility for substantive judgments."); *Federal Power Comm'n v. Transcontinental Gas Pipe Line Corp.*, 423 U.S. 326, 333–34, 96 S.Ct. 579, 46 L.Ed.2d 533 (1976) (" 'The Court, it is true, has power 'to affirm, modify, or set aside' the order of the Commission 'in whole or in part.' ... But that authority is not power to exercise an essentially administrative function.' ") (quoting *Federal Power Comm'n v. Idaho Power Co.*, 344 U.S. 17, 21, 73 S.Ct. 85, 97 L.Ed. 15 (1952)). We also take note, as held in *Weil v. Fritz*, 572 F.2d 856, 863, 196 USPQ 600, 606 (CCPA 1978), that the "applicant's oath is not a requirement of § 112, first paragraph, but of 35 U.S.C. § 115; therefore, the sufficiency of [the prior] oath is not material under § 120."

We discern no reversible error in the grant to Boone of the benefit of his chain of filings.

III

BOONE'S CROSS–APPEAL

The Board declined to enter judgment in favor of Boone, and entered judgment against Boone based on his request that his application be converted into a Statutory Invention Registration (SIR). Boone appeals the Board's refusal to rule on the patentability of his claims, which had been rejected on the ground of double patenting, and states that the Board erred in its refusal to enter judgment that the issue of priority was decided in his favor.

[16] At the hearing before the Board Boone renewed his request that the '541 application be converted into a Statutory Invention Registration in accordance with 35 U.S.C. § 157. The SIR permits an inventor to forego the grant of a patent while preserving the opportunity to contest priority through interference proceedings. The statute provides:

35 U.S.C. § 157. Statutory invention registration

(a) Notwithstanding any other provision of this title, the Commissioner is authorized to publish a statutory invention registration containing the specification and drawings of a regularly filed application for a patent without examination if the applicant—

(1) meets the requirements of section 112 of this title;

(2) has complied with the requirements for printing, as set forth in regulations of the Commissioner;

(3) waives the right to receive a patent on the invention within such period as may be prescribed by the Commissioner; and

(4) pays application, publication, and other processing fees established by the Commissioner.

* * * * * *

(c) A statutory invention registration published pursuant to this section shall have all of the attributes specified for patents in this title except those specified in section 183 and sections 271 through 289 of this title. A statutory invention registration shall not have any of the attributes specified for patents in any other provision of law other than this title.... The invention with respect to which a statutory invention certificate is published is not a patented invention for purposes of section 292 of this title.

The inventor of the SIR has "the same rights that a patent provides to prevent others from patenting the invention." *Section–by–Section Analysis: Patent Law Amendments of 1984*, 130 Cong. Rec. H10525 (Oct. 1, 1984), *reprinted in* 1984 U.S.C.C.A.N. 5827, 5828. The inventor preserves the ability to protect the right to practice his own prior invention as against any later inventor, while foregoing the right to exclude others even if he is the prior inventor. Thus the SIR affords an inventor the possibility of securing the defensive aspects of a patent by obtaining the right to contest priority, while agreeing to publish the technology, thereby benefitting the public. *Id.*

[17] Boone moved for permission to convert his '541 application to a SIR, after Boone had initiated this interference with

Hyatt and Boone's '541 application was rejected, on Hyatt's motion, on the ground of double patenting. Boone argues that the conversion of the '541 application to the SIR removed the only obstacle to patentability raised by the double patenting rejection, *i.e.* that of extension of effective patent life, because the SIR—since it is not an enforceable patent—would not effectively extend the patentee's right to exclude. Boone argues that he is entitled to a decision as to patentability although he will not obtain a patent.

The Board did not err in declining to rule on this issue in view of Boone's requested conversion to a SIR. Although Boone states that he is free to withdraw the SIR application at any time until the PTO has given notice of the intent to publish it, the intervening event of the interference proceeding has eliminated this option. Although administrative flexibility to accommodate changed circumstances or interests is a benefit of agency practice, there is rarely room for a complete change in position after the contrary position had achieved its purpose in a contested situation. We draw analogy to the rules of integrity in judicial proceedings. *See, e.g., Davis v. Wakelee,* 156 U.S. 680, 689, 15 S.Ct. 555, 39 L.Ed. 578 (1895) ("[W]here a party assumes a certain position in a legal proceeding, and succeeds in maintaining that position, he may not thereafter, simply because his interests have changed, assume a contrary position, especially if it be to the prejudice of the party who has acquiesced in the position formerly taken by him."); *cf. U.S. Philips Corp. v. Sears, Roebuck & Co.,* 55 F.3d 592, 596–97, 34 USPQ2d 1699, 1702–03 (Fed.Cir.1995) (equity holds a party to a position on which it prevailed).

The Board has instructed that Boone's application be examined for the purpose of publication as a SIR. Indeed, Boone has repeated on this appeal that he has no objection to this procedure. In view of Boone's action in requesting conversion to a SIR and the ensuing proceedings, the Board did not err in holding that Boone is not entitled to a patent on the '541 application. However, the patent interference statute requires the Board to determine which party has prevailed on the issue of priority. 35 U.S.C. § 135(a) ("The Board of Patent Appeals and Interferences shall determine questions of priority....").

[18, 19] Priority issues that have been fully developed and presented for decision should be decided. *See Guinn v. Kopf,* 96 F.3d 1419, 1422, 40 USPQ2d 1157, 1159 (Fed. Cir.1996). Indeed, the Board did decide priority, for the Board held that Hyatt was not entitled to the benefit of his '881 application date, and confirmed that Boone was entitled to his '565 application date. The Board's reason for refusing to recognize Boone's status as prior inventor was that Boone "was not entitled to a patent by express waiver of that right," citing 35 U.S.C. § 157(a)(3). However, the SIR waiver does not affect the adjudication of priority in resolution of the interference proceeding. The Board's statement, in its reconsideration decision, that it could not adjudge Boone to be prior inventor without also holding that Boone was entitled to a patent, citing 37 C.F.R. § 1.658(a), is an unwarranted reading of the regulation and is unsupported by the statute. Although the Board correctly ruled that Boone was not entitled to a patent, that ruling is not inconsistent with an adjudication of priority. Thus the judgment is modified to state that priority as to the count is awarded to Boone.

SUMMARY

The Board's decision that Hyatt is not entitled to the priority date of the '881 application as to the subject matter of the count is affirmed, as is the Board's decision that Boone is not entitled to a patent on this subject matter. However, judgment of priority in the interference contest shall be entered in favor of Boone.

No costs.

AFFIRMED, MODIFIED IN PART.